

FDA Advisory Committee Briefing Document

NDA #202-008

Florbetapir F18 Injection

Advisory Committee Meeting of January 20, 2011



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1. EXECUTIVE SUMMARY

1.1. Alzheimer's Disease and related pathology

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, currently affecting approximately 5 million people and costing \$172 billion per year in medical care in the US alone. Furthermore, AD is a disease of the aged, and it is expected to more than double in prevalence and in the costs of care over the next 20 years as the USA population ages. (http://www.alz.org/alzheimers_disease_facts_figures.asp).

Although the etiology of AD has not been definitively established, converging evidence suggests that β -amyloid aggregates play an important role in the pathogenesis of the disease. Regardless of the etiology, accumulation of the A β peptide to β -amyloid fibrils and neuritic β -amyloid plaques is one of the hallmarks of AD and is a defining component of the neuropathological criteria for autopsy-based diagnosis.^{1,2} Unfortunately the diagnosis and treatment of AD have been hampered by the absence of reliable non-invasive biomarkers for this underlying β -amyloid pathology. Clinical diagnosis based on consensus criteria is 70 – 80% accurate by comparison to the truth standard of pathology at autopsy.³ Furthermore, approximately 10% of the community dwelling elderly population have undiagnosed dementia,^{4,5} and community physicians may fail to diagnose up to 33% of mild dementia cases.⁵ Moreover, patients with non-AD causes of dementia are frequently misdiagnosed with AD, and the specificity of a clinical diagnosis of probable-AD is only approximately 70%.⁶ A reliable biomarker might also aid prognostic evaluation by documenting the presence or absence of Alzheimer's disease related pathology. In this context, recent proposals (e.g. Dubois et al⁷ and draft DSM V diagnostic criteria as well as proposed criteria from the National Institute on Aging and Alzheimer's Association work groups (http://www.alz.org/research/diagnostic_criteria/)) to include pathologically-linked biomarkers in the clinical diagnostic criteria reflect the medical need to reduce the frequency of false positive diagnoses and increase the validity of a clinical diagnosis of AD.

Based on the well accepted criteria for the neuropathological diagnosis of AD, the use of a test to rule-out the presence of pathologically significant levels of β -amyloid in subjects with clinical signs and symptoms of cognitive impairment would, effectively, rule out the diagnosis of AD. Such a test would then lead to more careful evaluation and appropriate treatment for alternative causes of cognitive deficits (e.g. vascular dementia, dementia with Lewy bodies, Parkinson's dementia, geriatric depression, or medication induced impairments). In addition, the use of a test which could reliably detect the presence of abnormal levels of β -amyloid pathology in subjects with signs and symptoms of cognitive impairment would lead to the identification of patients who warrant more detailed work-up for the possible diagnosis of AD.

Florbetapir F 18 (USAN/INN) is a novel 18F labeled tracer, discovered at the University of Pennsylvania⁸ which has been developed by Avid Radiopharmaceuticals and has shown promise for imaging β -amyloid aggregates in the human brain by positron emission tomography (PET).⁹ This PET imaging agent has demonstrated high affinity ($K_d=3.7$ nM) and selective binding to human β -amyloid aggregates, with no or very low affinity for common CNS receptors and other common neuropathologic targets such as neurofibrillary tangles.¹⁰

The overall development program which Avid Radiopharmaceuticals has completed for this NDA supports the conclusion that florbetapir-PET imaging is both safe and effective for the detection of β -amyloid aggregates in the human brain during life. The data reported in this NDA show specifically that florbetapir-PET is: 1) highly correlated with post-mortem histopathological measurements of β -amyloid, 2) is clinically reliable (i.e. has high specificity) for ruling-out significant β -amyloid pathology, 3) correlated with known clinical/epidemiological risk factors for brain amyloid, and 4) is well-tolerated and associated with a low frequency of mild and transient adverse events.

1.2. Proposed Indication and Usage

A New Drug Application for florbetapir F 18 is undergoing review by the U.S. Food and Drug Administration and has been assigned a “Priority Review” classification, as the product meets an unmet medical need. The florbetapir application will be discussed at the Peripheral and Central Nervous System Advisory Committee Meeting on January 20, 2011.

The proposed NDA indication for florbetapir is:

“Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β -amyloid in the brain.”

1.3. Overview of Clinical Efficacy for NDA 202-008, Florbetapir F 18

The focus of the florbetapir F 18 development program and this New Drug Application (NDA) was to establish the relationship between amyloid burden, as evidenced on the PET image, and the underlying true amyloid burden determined by postmortem histopathology. Four lines of evidence for the effectiveness of florbetapir-PET are provided in the NDA:

- **Florbetapir-PET signal correlates to amyloid histopathology present at autopsy.** The pivotal trial (Study ^{18}F -AV-45-A07 [A07]) demonstrated that there is a strong, statistically significant correlation between the level of cortical tracer binding in the PET image and actual β -amyloid levels measured post mortem by quantitative immunohistochemistry (IHC) or silver staining (Bielschowsky).
- **Florbetapir-PET scans are negative in subjects without amyloid pathology.** The pivotal Phase III trial (Study A07) has also demonstrated the high specificity of florbetapir-PET. Integration of data across all studies further supports the specificity conclusion of the pivotal clinical trial.
- **Florbetapir-PET results correlate with known clinical/epidemiological risk factors for brain amyloid.** Phase I and II trials demonstrated that the florbetapir-PET signal correlates with clinical diagnosis, age, ApoE genotype, and cognitive performance—all parameters known to be associated with increased prevalence of underlying A β pathology.
- **Florbetapir F 18 has a high affinity and selectivity for β -amyloid.** Nonclinical studies provide important supportive data that: (1) florbetapir F 18 binds to β -amyloid with high affinity, (2) florbetapir F 18 labeled amyloid plaques can be co-labeled with thioflavin, (3)

the density of florbetapir F 18 autoradiography signal is strongly correlated with the amount of β -amyloid detected by quantitative IHC, and (4) florbetapir F 18 radiolabeling of human brain tissue sections is highly specific for β -amyloid pathology and is not seen in tissue from subjects with neurological diseases with non- β -amyloid pathology (e.g. tangles).

1.4. Overview of Clinical Safety for NDA 202-008, Florbetapir F 18

Florbetapir-PET was well tolerated with the most common AE of headache occurring in less than 2% of subjects. Other notable AEs were likely related to the procedure of IV injection (<1% of subjects with injection site bleeding, bruising or pain) or to the PET-procedure (musculoskeletal pain in 0.8% of subjects).

There were a few small, statistically significant changes in lab parameters and vital signs, but most appeared not clinically significant and most were likely procedural in nature (e.g., changes in pulse and blood pressure at 75 minutes, when the patient finished the PET procedure) or were likely artifactual (e.g., systematic differences in methods for drawing labs [catheter vs. butterfly]). No changes in safety labs or vital sign measurements suggested a specific safety concern due to the administration of the study drug.

There was no safety signal specifically observed in cognitively impaired subjects as compared to cognitively normal subjects or as compared to the whole safety population. In addition, the drug was well tolerated even in the Autopsy Cohort end-of-life population enrolled in study A07, which had many severe concomitant medical illnesses.

Subpopulation analyses were conducted to look for any safety effects related to gender, geriatric versus non-geriatric subpopulations, in white versus non-white subjects, in subjects taking AD medications, and in subjects with cardiac rhythm disturbances. There were no remarkable or consistent changes in safety parameters observed in any of these subpopulations.

To date, florbetapir has now been used for research purposes in more than 2,000 patients across approximately 100 imaging sites on 5 continents. Ongoing research studies include numerous therapeutic pharmaceutical trials (where florbetapir is used as a biomarker for patient selection or surrogate endpoint), longitudinal studies of aging and disease (including the Alzheimer's disease Neuroimaging Initiative, or ADNI), and investigator initiated studies.

1.5. Guidance for Use

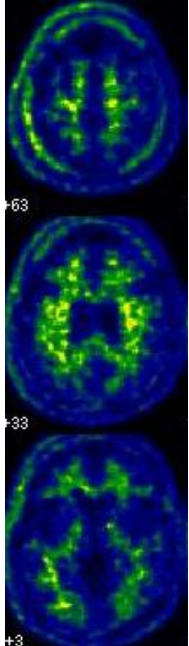
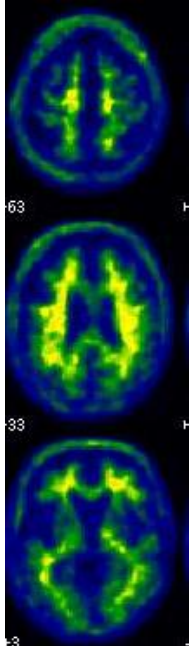
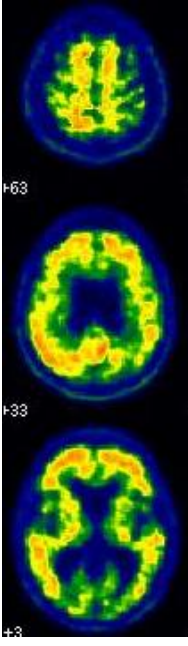
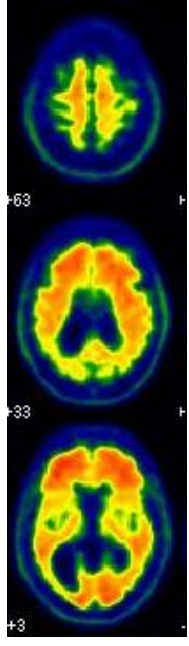
The recommended dose for Florbetapir F 18 Injection is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of ≤ 10 mL. This dose, in a blinded read of florbetapir-PET scans, provided consistent good quality PET images from a 10 minute scan acquisition. No special preparation of the patient is needed. The dose is administered by intravenous injection, followed by a flush of 0.9% Sodium Chloride Injection to ensure full delivery.

Both binary (+ / -) and semi-quantitative visual interpretation of florbetapir-PET images were conducted in clinical trials. The semi-quantitative (0-4 rating) visual interpretation of florbetapir-PET images performed in the Phase III trial to evaluate the correlation of PET amyloid signal in the cortical grey matter with histopathological measures of β -amyloid demonstrated a

statistically-significant positive correlation for all three blinded readers. Since the expected primary use in clinical practice will be simply to determine the presence or absence of pathologically significant levels of β -amyloid, it is recommended that a simple binary assessment of florbetapir-PET images is adequate for routine clinical use. Phase II and Phase III data demonstrated that the binary (i.e. positive or negative) read of florbetapir-PET scans provides a reliable and accurate assessment of the presence or absence of pathologically significant levels of β -amyloid in the brain. The high specificity of the florbetapir-PET scan observed in the Phase III A07 trial using the binary image rating score indicates that a negative florbetapir-PET scan is consistent with the absence of significant levels (e.g. CERAD neuritic plaque density of none to sparse) of β -amyloid levels in the brain.

It is recommended that a new user of florbetapir F 18 for amyloid PET imaging should receive training in image acquisition and interpretation. Avid proposes to make training modules, including images of cases with autopsy-verified amyloid levels from the Phase III study subjects, available at a training website ([Table 1](#)). Physicians should complete the training modules provided on this website or complete similar training available from other professional organizations or medical education providers.

Table 1: Representative Florbetapir-PET Images and Neuropathology Data from A07 Phase III Trial

Visual Read	Negative		Positive	
				
CERAD IHC%	None 0.0%	Sparse 0.47%	Moderate 1.11%	Frequent 9.4%

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
^{18}F	fluorine-18
μg	microgram
μL	microliter
^{18}F -AV-45	Florbetapir F 18
A β	beta amyloid
A β +	β -amyloid positive
A β -	β -amyloid negative
AC	Advisory Committee
AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Clinical Studies Consortium Activities of Daily Living
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive
ANOVA	analysis of variance
ApoE	apolipoprotein E genotype
CA	Cognitive Assessment
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	confidence interval
CRO	clinical research organization
CT	computed tomography
CSF	cerebrospinal fluid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSS	digit symbol substitution
ECG	electrocardiogram
FDA	Food and Drug Administration
FDG PET	^{18}F -fluorodeoxyglucose positron emission tomography
FTD	frontal temporal dementia
GDS	Geriatric Depression Scale
HC	healthy controls
ICC	intraclass correlation coefficient
IHC	immunohistochemistry

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Abbreviation	Definition
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	intravenous
kg	kilograms
MBq	megabecquerel
mCi	millicurie
MCI	mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
msec	milliseconds
mSv	millisievert
NDA	New Drug Application
NIA	National Institute on Aging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association
NPV	negative predictive value
ODD	other dementing disorders
OHC	older healthy controls, cognitively normal subjects ≥ 50 years of age
PET	positron emission tomography
PIB	Pittsburgh compound B
PK	pharmacokinetic
PPV	positive predictive value
SD	standard deviation
SPM	statistical parametric mapping
SUV	standardized uptake value (= activity concentration (Bq/cc) x subject weight (g)/injected dose (Bq))
SUVR	standardized uptake value ratio (region/cerebellum)
VF-A	Verbal Fluency – Animal
VF-V	Verbal Fluency – Vegetables
WLM-I	Wechsler Logical Memory test–immediate paragraph recall
WLM-II	Wechsler Logical Memory test–delayed paragraph recall
YHC	young healthy controls, cognitively normal subjects < 50 years of age

4. RATIONALE: NEED FOR IN VIVO DETECTION OF AMYLOID

Currently, Alzheimer's disease (AD) is considered to be a clinico-pathologic disease entity, with definitive diagnosis requiring both a particular clinical phenotype and specific neuropathological changes (including significant levels of brain neuritic amyloid plaque) measured at autopsy. Based on the definitions of AD endorsed by the American Academy of Neurology, American Psychiatric Association (DSM-IV) and others, patients without abnormal amyloid plaque levels do not meet criteria for AD (see [Table 2](#)).

Table 2: Guidelines for Clinical Diagnosis of AD

Organization	Reference	Guideline
American Psychiatric Association	APA Practice Guideline for the Treatment of Patients with AD and Other Dementias, 2 nd Ed., Rabins et al., 2007.	Definitive diagnosis requires clinical and pathological findings: "A definitive diagnosis of AD requires both the clinical syndrome and microscopic examination of the brain at autopsy, at which time the characteristic plaques and neurofibrillary tangles widely distributed in the cerebral cortex will be seen."
American Psychiatric Association	DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4 th Ed., 2000.	Definitive diagnosis requires pathological confirmation: "Because of the difficulty of obtaining direct pathological evidence of the presence of AD, the diagnosis can be made only when other etiologies of dementia have been ruled out."
United States Department of Health and Human Services	Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on AD, McKhann et al., 1984	Definitive diagnosis requires clinical and pathological findings: "Criteria for diagnosis of DEFINITE Alzheimer's disease are: the clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy." "A diagnosis of definite AD requires hisopathologic confirmation."
American Academy of Neurology	Practice Parameter: Diagnosis of dementia (an evidence-based review): Report of the Quality Standards Subcommittee, Knopman et al., 2001.	Neuropathology is the gold standard for diagnosis: "There are 13 studies, 3 Class I and 10 Class II, that have addressed the diagnostic accuracy of the clinical diagnosis of AD using neuropathologic confirmation as the 'gold standard'."
American Geriatrics Society	Clinical Practice Guidelines: Early Detection of Dementia, 2002.	Definitive diagnosis requires clinical and pathological findings: Guidelines are abstracted from the American Academy of Neurology's dementia guidelines, described above. "The NINCDS-ADRDA criteria ... should be routinely used"
College of American Pathologists (under auspices of AMA)	Practice Guidelines for Autopsy Pathology, James Powers, Arch Pathol Lab Med, 1995.	Definitive diagnosis requires presence of amyloid plaques: "This grade [of plaques] is then correlated with the patient's age to arrive at an age-related plaque score, which is combined with the clinical history (presence or absence of dementia) to determine the diagnosis."
CERAD (Consortium to Establish a Registry for AD)	The Consortium to Establish a Registry for AD. Part II. Standardization of the neuropathologic assessment of AD, Mirra et al., Neurology, 1991.	Definitive diagnosis requires high (age-adjusted) abundance of amyloid plaques: "The age-related plaque score is integrated with the presence or absence of a clinical history of dementia to arrive at a diagnostic level of certainty with regard to AD."
National Institute on Aging & Reagan Institute Working Group	Consensus Recommendations for the Postmortem Diagnosis of Alzheimer's Disease, Neurobiology of Aging, 1997.	Definitive diagnosis requires high (age-adjusted) abundance of amyloid plaques and neurofibrillary tangles: "There is a high likelihood that dementia is due to AD lesions when the postmortem brain shows the presence of both neuritic plaques and neurofibrillary tangles in neocortex." There is a low probability of AD in subjects with low levels of amyloid plaques: "There is a low likelihood that dementia is due to Alzheimer's disease lesions when the postmortem brain shows neuritic plaques and neurofibrillary tangles in a more limited distribution and/or severity (i.e. CERAD infrequent, and Braak and Braak Stage I/II)."

Because assessment of AD pathology cannot typically be done in life (except in rare cases of brain biopsy), criteria for clinical diagnosis of “probable AD” or “possible AD” have been developed, however such diagnoses are only 81% sensitive and 70% specific by comparison to the truth standard of pathology at autopsy.^{3,5,11} Moreover, these criteria are often applied late in the disease course, and physicians may fail to diagnose up to 33% of mild dementia cases.⁶ In addition, patients with non-AD causes of dementia are frequently misdiagnosed with AD, and peer reviewed literature confirms that 10 to 23% of all patients that receive a diagnosis of AD do not have AD pathology at autopsy (Table 3).

Table 3: Frequency of false positive clinical diagnosis of AD, confirmed by autopsy.

Study	Summary	False Positive Rate of Clinical Diagnosis
Lim et al., <i>J Am Geriatr Soc.</i> 1999; 47: 564-569	Of 100 patients with clinical diagnosis of possible or probable AD followed to autopsy, 20 had a final diagnosis that did not include AD – none of these had neuritic plaques (NPs)	20% of patients with “possible or probable AD” did not have AD at autopsy
Victoroff et al., <i>Am J Psychiatry</i> 1995; 152: 1476-1484	Of 163 patients with clinical diagnosis of possible or probable AD followed to autopsy, 29 had a final diagnosis that did not include AD – none of these had NPs	18% of patients with “possible or probable AD” did not have AD at autopsy
Klatka et al., <i>Arch Neurol.</i> 1996; 53: 35-42	Of 170 patients with a clinical diagnosis possible of probable AD followed to autopsy, 21 had a final diagnosis that did not include AD – none of these had NPs	12% of patients with “possible or probable AD” did not have AD at autopsy
Wade et al., <i>Arch Neurol.</i> 1987; 44: 24-29	Of 55 patients with a clinical diagnosis of DAT or DAT + MID followed to autopsy, 10 had a final diagnosis that did not include AD (3 of these 10 had some senile plaques)	18% of patients with “DAT or DAT + MID” did not have AD at autopsy
Pearl et al., <i>S Med J</i> , 1997; 90: 720-722	Of 234 patients with clinical diagnosis of AD or mixed AD followed to autopsy, 53 patients had a final diagnosis that did not include AD – none of these had NPs	23% of patients with AD or AD + vascular dementia did not have AD at autopsy
Jobst et al., <i>Int Psy Ger</i> 1999; 10: 271-302	Of 92 patients with clinical diagnosis of probable or possible AD followed to autopsy, 15 did not have AD at autopsy	16% of patients with clinical AD did not have AD at autopsy
Massoud et al., <i>Arch Neurol</i> 1999; 56: 1368-1373	Of 60 patients with clinical diagnosis of probable or possible AD followed to autopsy, 6 did not have AD as a neuropathologic diagnosis. None of these had NPs	10% of patients with possible or probable AD did not have AD at autopsy
Ranginwala et al., <i>Am J Geriatr Psych</i> 2008; 16: 384-388	Of 225 subjects with a clinical diagnosis that included AD followed to autopsy, 31 did not have AD as a neuropathologic finding. All were plaque negative	14% of patients with AD as a clinical diagnosis did not have AD at autopsy
Gearing et al., <i>Neurology</i> 1995; 45: 461-466	Of 106 patients with a clinical diagnosis of probable or possible AD followed to autopsy, 14 did not have AD as the neuropathologic diagnosis (2 of the 14 had moderate plaques)	13% of patients with possible or probable AD did not have AD at autopsy

The high false positive rate of clinical diagnosis of AD means that 10 - 23% of patients clinically diagnosed with AD actually have another underlying cause of dementia, but are unfortunately misdiagnosed as having AD.

Given the short-comings of current consensus criteria for the clinical diagnosis of AD, there has been an effort by the AD community to update diagnostic criteria to incorporate biomarker evidence of AD pathology into the clinical diagnosis:

1. The American Psychiatric Association has published online a draft DSM-V, containing new criteria for diagnosis of AD (which update the DSM-IV criteria). The DSM-V criteria, citing the “modest predictive value of the clinical picture alone”, now require the use of biomarkers (such as an amyloid PET scan or CSF measures) which detect “an underlying AD pathology”, in order to diagnose AD in the mild (minor) stage.
2. Updates to the NINCDS-ADRDA criteria for clinical diagnosis of AD have recently been proposed in draft form by the National Institute of Aging (NIA) working together with the Alzheimer’s Association. The draft guidelines place a heavy reliance on the use of biomarkers for AD pathology, particularly detection of amyloid on PET scan, which they suggest may provide the earliest evidence of AD pathology, and are required to diagnose AD in the mild stage. Negative AD pathology biomarkers make the diagnosis of AD unlikely.
3. The International Working Group published new research criteria for AD in 2007 (Dubois, Lancet Neurology), and updated these criteria in 2010 (Dubois, Lancet Neurology). Under these criteria, diagnosis of AD requires biomarker evidence of AD brain pathology (such as amyloid PET scan), and subjects who are biomarker negative should not be diagnosed with AD.

Thus, even before the availability of any standardized FDA-approved test for the in-vivo detection of AD pathology, each of the major new guidelines under consideration for the diagnosis of AD have recommended the use of such a test for AD pathology to aid in the diagnosis of patients, and in many cases these proposed guidelines even require biomarker evidence of AD pathology before a clinical diagnosis of dementia can be made. Importantly, these criteria all specifically note the promise of amyloid PET imaging for the in-life detection of AD pathology. Thus, the goal of this NDA was to validate florbetapir F18 as safe and effective for the in vivo detection of amyloid pathology by Positron Emission Tomography (PET). The proposed indication for florbetapir in the United States is:

“Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β -amyloid in the brain.”

5. SUMMARY OF CLINICAL SAFETY AND EFFECTIVENESS

5.1. Overview of florbetapir F 18 studies

The clinical development program consisted of 7 clinical studies designed to evaluate the safety and effectiveness of florbetapir. The objectives of the florbetapir development program were to:

- Characterize the in-vitro and ex-vivo binding characteristics of florbetapir F 18
- Understand the time course of florbetapir-PET and to recommend appropriate imaging timeframes and image acquisition parameters
- Identify a radioactive dose of florbetapir F 18 that provides acceptable image quality and reliable evaluation
- Demonstrate the reliability of florbetapir-PET image evaluation
- Evaluate the relationship between florbetapir-PET results and known risk factors for pathologically significant levels of β -amyloid aggregates in the brain
- Evaluate the correlation between florbetapir-PET image measurements of cortical amyloid levels and histopathological measurements of β -amyloid as the reference standard
- Demonstrate the clinical safety of florbetapir F 18 under its prescribed conditions of use.

Across all of the completed clinical studies included in the NDA, 496 subjects received at least one dose of florbetapir. The 496 subjects comprise the overall safety population, and 487 subjects comprise the florbetapir efficacy population. [Table 4](#) presents a summary of the studies in the florbetapir clinical development program, including the primary objectives addressed and the key results obtained.

Table 4: Description of the Primary and Supportive Clinical Efficacy Studies

Study ID, Phase	Study Drug Dose, Route, and Frequency, and Image Acquisition	Study Objectives	No. of Subjects Entered and Cohort Populations	Efficacy Results
A07, Ph III	370 MBq (10 mCi), IV, single dose 10 minute scan acquired 50 minutes post dose	Correlate brain imaging of β -amyloid plaque with histopathology at autopsy Evaluate the specificity of florbetapir in subjects expected to be negative for β -amyloid pathology. Evaluate safety	Total no. of subjects entered: 226 <u>Autopsy Cohort</u> : 152 35 completed and are in the efficacy group <u>Specificity Cohort</u> : 74 47 are in the primary efficacy group	<u>Autopsy Cohort</u> Significant correlation between: 1. PET visual read (0-4) and postmortem IHC (whole brain) 2. PET visual read of various regions (0-4) and postmortem IHC (regional) 3. PET visual read (0-4) and postmortem silver stain 4. PET quantitation (SUVR) and postmortem IHC 5. PET quantitation (SUVR) and postmortem silver stain <u>Specificity Cohort</u> 6. Observed rate of amyloid negative visual reads in YHC >90%
A05, Ph II	370 MBq (10 mCi), IV, single dose 10 minute scan acquired 50 minutes post dose	Differentiate healthy controls from subjects with a clinical diagnosis of AD or MCI, and evaluate safety Evaluate the relationship between Florbetapir-PET results and clinical/epidemiological risk factors for brain amyloid Evaluate reader training process Evaluate Safety	No. of subjects entered: 184 (45 AD, 60 MCI, 79 HC)	1. Correlation between PET imaging and multiple measures that should be related to presence of amyloid pathology 2. Significant difference in mean SUVR and % of subjects with amyloid positive scans among AD, MCI, and HC 3. SUVR increased with age and the presence of an ApoE ϵ 4 allele 4. SUVR was correlated with cognitive performance in HC. Amyloid positive HC, while still performing in normal range, perform less well than amyloid negative HC

Table 4: Description of the Primary and Supportive Clinical Efficacy Studies (Continued)

Study ID, Phase	Study Drug Dose, Route, and Frequency, and Image Acquisition	Study Objectives	No. of Subjects Entered and Cohort Populations	Efficacy Results
A01, Ph I	370 MBq (10 mCi), IV, single dose 90 minute continuous scan	To compare uptake and distribution of study drug in AD and HC; PK; safety; and dosimetry in HC	No. of subjects entered: 32 (16 AD, 16 HC)	1. Significant difference in tracer uptake between AD patients and healthy volunteers. 2. Rapid washout from nontarget tissue. Stable imaging results from \approx 45 minutes to 90 minutes post dose
A03, Ph I	111 MBq (3 mCi) (N = 9) and 370 MBq (10 mCi) (N = 11), IV, single dose 90 minute continuous scan	To confirm the appropriate dose for future studies and evaluate safety	No. of subjects entered: 20 (9 AD, 11 HC)	1. Better image quality at 370 versus 111 MBq 2. No diagnostic difference between 370 MBq and 111 MBq 3. Clear difference in tracer uptake between AD patients and young HC at both 370 MBq and 111 MBq doses
A04, Ph I	370 MBq (10 mCi), IV, 2 doses within 4 weeks 20 minute scan 50 minutes post dose	To evaluate test-retest reproducibility of study drug for brain imaging of amyloid in HC and AD and safety	No. of subjects entered: 25 (15 AD, 10 HC)	1. High test-retest reproducibility in semi-quantitative visual read and SUVR 2. Clear difference in tracer uptake between AD patients and YHC 3. SUVR threshold calculated in Young Healthy Controls
A06	None	To compare visual read and SUVR values taken at 30 – 40 minutes post dose versus 50 – 60 minutes post dose	All subjects from Studies A01 and A03 with valid imaging data	1. No statistically significant differences between visual reads or SUVR values at 30 – 40 minute and 50 – 60 minute time points

Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; ApoE, apolipoprotein E genotype; CDR, Clinical Dementia Rating; HC, healthy controls; ; IV, intravenous; MCI, mild cognitive impairment; ODD, other dementing disorders; MMSE, Mini Mental State Examination; NINCDS, National Institute of Neurological and Communication Disorders; PET, positron emission tomography; PK, pharmacokinetic; SUVR, standardized uptake value ratio (region/cerebellum); YHC, young healthy controls.

5.2. Florbetapir-PET Efficacy

The primary efficacy of florbetapir was demonstrated in a single Phase III clinical study which enrolled two distinct analysis populations totaling 226 subjects. Two primary analysis endpoints were tested in this study. The results of this Phase III trial are supported by additional efficacy data obtained from five Phase I and II clinical studies, which also established the pharmacokinetics and pharmacodynamics of florbetapir-PET imaging.

5.2.1. Phase III AV-45-A07 Study

The Phase III Pivotal Study was a prospectively-designed imaging trial designed to:

1. Determine the correlation between measurements of cortical brain β -amyloid using florbetapir-PET imaging and the levels of β -amyloid measured by histopathology post mortem (Autopsy Cohort)
2. Confirm the specificity of florbetapir-PET imaging, using a cohort of individuals with a very low likelihood of having significant levels of β -amyloid in the brain based on their age, clinical history and absence of known risk factors¹² (Specificity Cohort).

Objective

The primary hypothesis for the Autopsy Cohort was that there would be a significant positive correlation between the blinded reader semi-quantitative rating of cortical brain β -amyloid on the PET scan (median of 3 readers) and the average cortical β -amyloid, as determined post mortem by quantitative immunohistochemistry.

The primary hypothesis for the Specificity Cohort was that the observed specificity of the florbetapir-PET imaging would be $\geq 90\%$ (i.e., $\geq 90\%$ of the florbetapir-PET scans would be rated as amyloid negative on an independent blinded read, using the majority view of 3 readers) in a population of cognitively normal control subjects less than 40 years of age, who had no first degree relatives with Alzheimer's disease (AD), and who were not ApoE $\epsilon 4$ allele carriers.

Design

Study A07 was a multi-center, Phase 3 single dose study designed to compare florbetapir-PET images to amyloid pathology. All subjects received a 10 min PET scan, 50 min following a 370 Mbq (10mCi) IV dose of florbetapir. PET Images were attenuation corrected and fused with CT when PET/CT was used.

Subjects in the Autopsy Cohort were followed until death for autopsy evaluation. Study A07 employed a front runner design using the first six subjects coming to autopsy for method evaluation. The next 29 subjects that came to autopsy comprised the primary efficacy population.

Subjects in the Specificity Cohort were imaged using parameters identical to those used in the Autopsy Cohort.

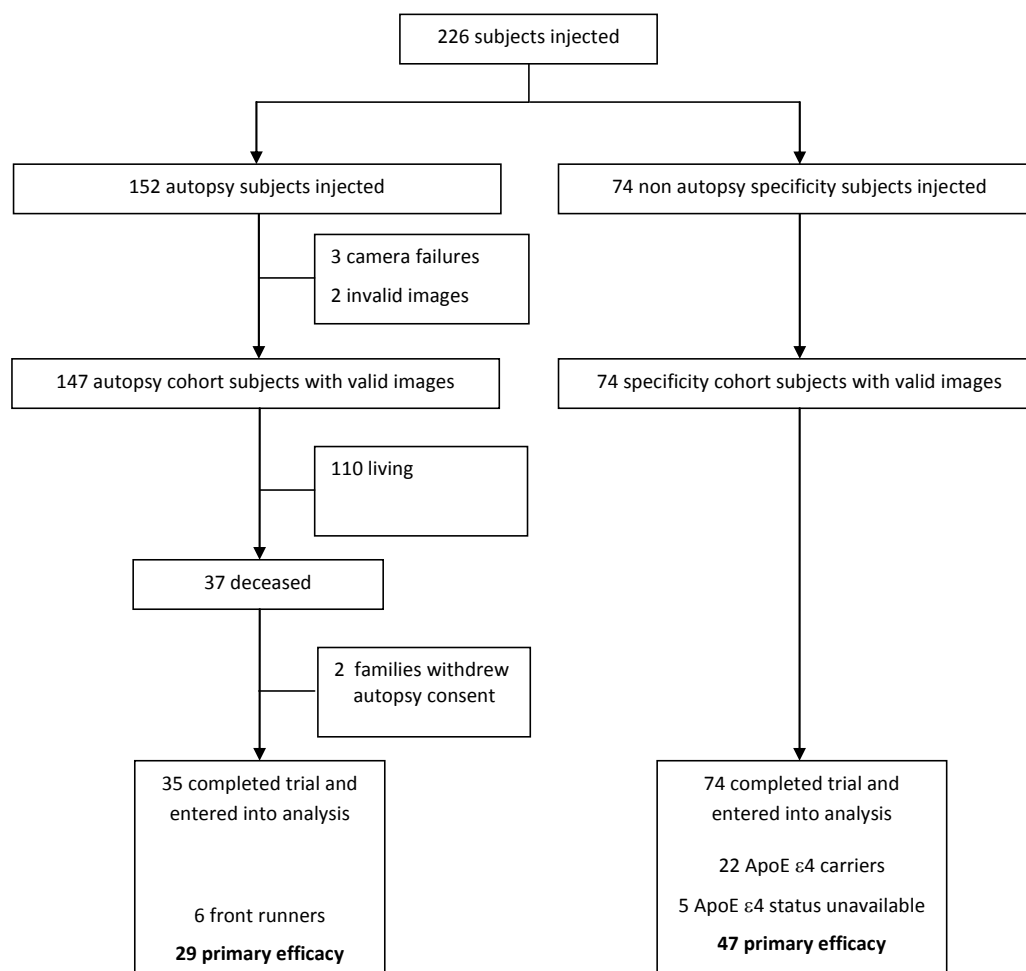
Population and disposition

A total of 226 subjects were injected with florbetapir F18 in this study; 152 subjects in the autopsy cohort nearing the end-of-life (56 subjects with a clinical diagnosis of AD, 25 subjects with MCI, 21 with other dementing disorders and 50 cognitively normal subjects) and 74 subjects (all cognitively normal) were enrolled in the specificity cohort.

At the end of the study, 110 subjects in the autopsy cohort were alive, and 37 subjects had died. Of the 37 subjects who died, consent to perform the autopsy was withdrawn for 2 subjects by their families. Thus, there were 35 subjects in the autopsy cohort who completed the trial and had both florbetapir-PET and histopathology data available for analysis. Of these 35 subjects, 6 were front-runners and 29 comprised the efficacy population for the primary correlation analysis. See [Figure 1](#).

Seventy-four subjects in the specificity cohort were injected with florbetapir F 18 and had valid images. All 74 subjects completed the trial and had data available for analysis. A total of 27 subjects were excluded from the primary efficacy population because they were either ApoE ϵ 4 allele carriers (22 subjects) or their ApoE ϵ 4 genotype was not available (5 subjects). Thus, a total of 47 control subjects comprised the primary efficacy population for the specificity analysis. See [Figure 1](#).

Figure 1: A07 Subject Disposition



Source: A07 Clinical Study Report

Methods of Image and Pathology Evaluation:

Image Evaluation

For the primary analyses, the PET images were evaluated visually using a semi-quantitative image rating scale for the autopsy cohort and were evaluated qualitatively (amyloid-positive or amyloid-negative) for the specificity cohort. All blinded reads were conducted on PET images that were presented in a randomized fashion and all images were evaluated by readers after a standard training session and without access to any clinical or pathological information.

- For semi-quantitative image reads (autopsy cohort correlation analysis), the visual semi-quantitative rating was performed by three independent readers. Each reader rated the degree of florbetapir retention in the cortical grey matter on a scale from 0 (no amyloid) to 4 (high levels of β -amyloid deposition), and the median score of the 3 readers was used in the primary analysis.

- For the qualitative blinded read (specificity cohort), a new group of three readers classified images as either positive for β -amyloid ($A\beta$ +, AD-like) or amyloid negative ($A\beta$ -, not AD like). In order to minimize bias, the specificity cohort images were randomly mixed with 40 presumed positive scans (the first 40 scans rated 2, 3, or 4 in the autopsy cohort blinded read). The majority qualitative read result of the blinded readers was the primary PET efficacy endpoint for the specificity evaluation.

For several exploratory analyses, florbetapir-PET images were evaluated quantitatively using a semi-automated computerized analysis. Using previously established methods (from Phase I studies) for the quantitative evaluation, each PET scan was spatially normalized to a standard atlas space using publically available software (Statistical Parametric Mapping 2, or commonly known as SPM2 available at <http://www.fil.ion.ucl.ac.uk/spm/doc/>) using a predefined target scan. After quality control, atlas based regions-of-interest for 6 cortical areas (frontal, anterior cingulate, temporal, parietal, posterior cingulate and precuneus) and the whole cerebellum were applied to extract the underlying regional mean counts. Each cortical regional SUV was divided by the cerebellar mean count to generate mean count ratios (or SUVR). The mean of the SUVRs for the 6 cortical target regions was then generated (the cortical SUVR) and used to represent a quantitative measure of brain florbetapir retention in exploratory analyses. Phase I studies have shown that the SUVR has very high scan-to-scan reproducibility and in Phase II studies highly correlates to visual interpretation.

All image evaluations and analyses were completed at an Imaging Core Lab which had no access to any histopathological information.

Autopsy Reference Standards

The reference standard for evaluating the correlation of florbetapir-PET to actual levels of amyloid was the histopathological measurement of β -amyloid. Amyloid burden at autopsy was evaluated in two ways. For the pre-specified primary analysis, global β -amyloid was measured by quantitative immunohistochemistry (IHC). Additionally, amyloid plaque counts, as evidenced on Bielschowsky silver staining were assessed using a modified CERAD scoring system.

The reference standard for evaluating the specificity of florbetapir-PET was the presumed negative status for amyloid pathology for young healthy subjects based on their age and lack of other amyloid risk factors¹².

- For the automated immunohistochemistry process, tissue sections were prepared from each of the six primary analysis regions and the percent area occupied by β -amyloid was measured. Multiple tissue sections from each region were averaged to provide a global assessment. This global cortical amyloid burden measured by IHC was the primary outcome variable.
- For the specificity analysis, young, cognitively normal controls less than 40 years of age, who had no first degree relatives diagnosed with AD, and who were not ApoE ϵ 4 allele carriers, were used as the primary analysis population.
- For exploratory analyses, the neuropathologist reviewed a subset of tissue slides and provided the standard neuropathologic diagnosis using modified CERAD criteria. In these analyses the neuritic plaque count rating was converted to a CERAD score (see [Table 5](#)) and used as an alternative measure of cortical β -amyloid levels.

Table 5: CERAD Plaque Rating and Diagnosis

Modified CERAD Scoring		
Neuritic Plaque Counts	Modified CERAD Diagnosis	Regional Semi-quantitative CERAD Rating
<1	No AD	0 (none)
1-5	Possible	1 (sparse)
6-19	Probable	2 (moderate)
20+	Definite	3 (frequent)

Results

Demographics

Study A07 Demographics and baseline characteristics are summarized in [Table 6](#).

Table 6: Demographic Characteristics by Cohort

Characteristic	Autopsy Cohort		Specificity Cohort	
	Subjects Imaged N=152 ^a	Subjects with Autopsy N=29 ^b	Subjects Imaged N=74 ^a	Non-ApoE ε4 Carriers N=47 ^b
Age (years)				
Mean ± SD	78.1 ± 13.35	80.0 ± 13.19	26.6 ± 6.50	26.3 ± 7.17
Median	81.5	85.0	25.5	24.0
Range	38 to 103	55 to 103	18 to 50	18 to 50
Gender				
Male	71 (46.7%)	15 (51.7%)	48 (64.9%)	32 (68.1%)
Female	81 (53.3%)	14 (48.3%)	26 (35.1%)	15 (31.9%)
Race				
Caucasian	134 (88.2%)	26 (89.7%)	57 (77.0%)	36 (76.6%)
Black or African-American	10 (6.6%)	2 (6.9%)	6 (8.1%)	4 (8.5%)
Other	4 (2.6%)	1 (3.4%)	7 (9.5%)	4 (8.5%)
Asian	2 (1.3%)	0	4 (5.4%)	3 (6.4%)
Native American / Alaskan Native	2 (1.3%)	0	0	0
Ethnicity				
Non-Hispanic or Latino	139 (91.4%)	28 (96.6%)	69 (93.2%)	44 (93.6%)
Hispanic or Latino	13 (8.6%)	1 (3.4%)	5 (6.8%)	3 (6.4%)
Diagnosis				
Alzheimer's disease	56 (36.8%)	13 (44.8%)	0	0
Mild cognitive impairment	25 (16.4%)	2 (6.9%)	0	0
Other dementing disorder	21 (13.8%)	5 (17.2%)	0	0
No cognitive impairment	50 (32.9%)	9 (31.0%)	74 (100.0%)	47 (100.0%)
MMSE				
N	115	21	74	47
Mean ± SD	21.2 ± 9.34	19.9 ± 9.96	29.7 ± 0.57	29.8 ± 0.40
Median	25.0	23.0	30.0	30.0
Range	0 to 30	0 to 30	27 to 30	29 to 30
Interval between PET scan and death (months)				
Mean ± SD	--	3.2 ± 2.57	--	--
Interval between death and autopsy (hours)				
Mean ± SD	--	10.7 ± 7.95	--	--

Source: A07 Clinical Study Report

Abbreviations: SD = standard deviation

Percentages were calculated using the number of non-missing values in each cohort.

a) Safety population, b) Primary efficacy population

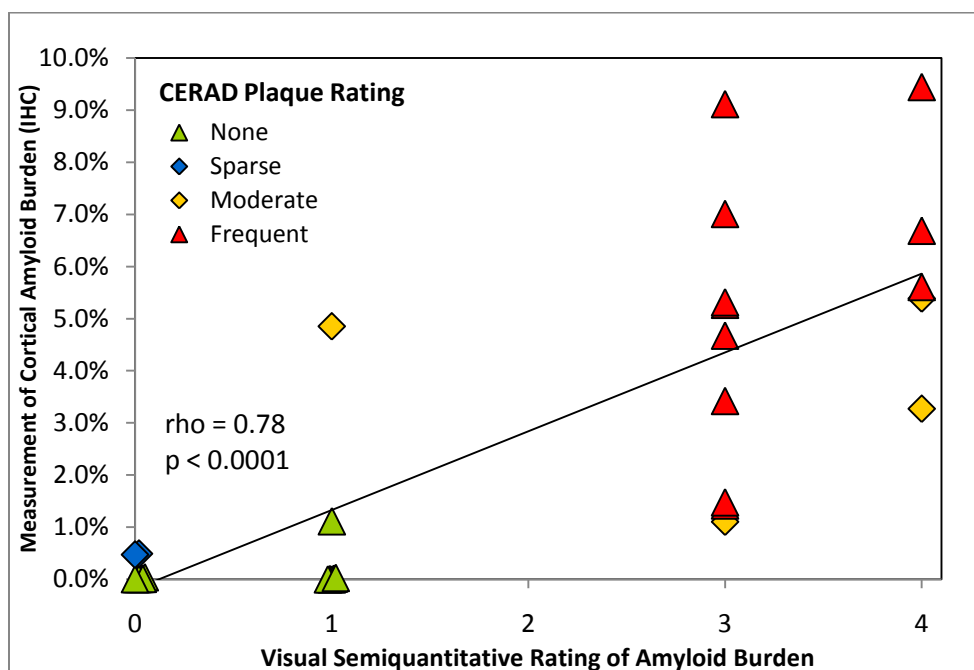
The age range in the autopsy cohort of study A07 (38-103) encompassed the age range of subjects expected to receive florbetapir in clinical practice. The mean age (78.1) was slightly older than might be expected in routine use due to the fact that this population was selected for patients in the last year of life. Cognitive status of these subjects ranged from cognitively normal through MCI to end stage AD, with approximately half of the AD patients being in the mild to

moderate range. In other respects the population was similar both to the populations in other trials and the expected clinical population.

Primary Efficacy Correlation Analysis

For the test of the first primary hypothesis, a strong, statistically significant correlation Spearman's rho ($\rho = 0.78$, $P < 0.0001$; 95% Confidence Interval [CI], 0.58 to 0.89) was observed between the semi-quantitative visual rating of β -amyloid levels on the florbetapir-PET image and the cortical β -amyloid levels as assessed by quantitative IHC post mortem. Figure 2 plots the median visual read versus IHC measured β -amyloid along with the CERAD plaque rating for each data point. All subjects with a CERAD rating of none/sparse were read as 0 or 1 on the PET scan, and with a single exception, subjects with more than sparse neuritic plaques were read as 3 or 4.

Figure 2: Correlation of Median Visual Blinded Read of Florbetapir-PET Scan with Immunohistochemistry Measurement of β -amyloid



In addition, strong correlations between florbetapir-PET measures of β -amyloid and neuropathology measures of β -amyloid at autopsy were observed ($P < 0.0001$) across all the different methods of evaluating the PET images (qualitative and semi-quantitative visual ratings and quantitative SUVR) and the different methods of quantitating β -amyloid at autopsy (IHC quantitation of A β and neuritic plaque density by silver staining) as well as in different brain regions (cortical average and 6 individual cortical regions). Table 7 provides a summary of the correlation analyses tested in Study A07. The correlation results were not significantly different when the 6 front runner subjects were included.

Table 7: Efficacy Measures in Study A07

	Primary Efficacy Cohort (N = 29)	
	Correlation	P value
Primary Measure		
Global Semi-quantitative PET vs IHC autopsy	$\rho = 0.78$	$P < 0.0001$
Secondary Measures (Regions)		
Frontal	$\rho = 0.69$	$P < 0.0001$
Anterior cingulate	$\rho = 0.74$	$P < 0.0001$
Parietal cortex	$\rho = 0.77$	$P < 0.0001$
Precuneus	$\rho = 0.75$	$P < 0.0001$
Posterior cingulate	$\rho = 0.70$	$P < 0.0001$
Temporal	$\rho = 0.68$	$P < 0.0001$
Exploratory Measures		
Global SUVR PET vs IHC autopsy	$\rho = 0.75$	$P < 0.0001$
Global Semi-quantitative PET vs Neuritic Plaque	$\rho = 0.71$	$P < 0.0001$
Global SUVR PET vs Neuritic Plaque	$\rho = 0.74$	$P < 0.0001$

In addition, the individual reader correlations between the semi-quantitative visual rating of β -amyloid levels on the florbetapir-PET image and the cortical β -amyloid levels as assessed by quantitative IHC post mortem also met the predefined primary endpoint as shown in [Table 8](#).

Table 8: Individual Reader Evaluation vs Immunohistochemistry

	Primary Efficacy Cohort (N = 29)	
	Correlation	P value
Global Semi-quantitative PET vs IHC autopsy		
Reader 1	$\rho = 0.73$	$P < 0.0001$
Reader 2	$\rho = 0.81$	$P < 0.0001$
Reader 3	$\rho = 0.65$	$P < 0.0001$

Primary Efficacy Specificity Analysis

For the test of the second primary hypothesis, the observed specificity of florbetapir-PET imaging in the Specificity Cohort was 100% (95% CI, 91% to 100%).

Moreover, the individual blinded reader results in the specificity cohort met the primary objective of $> 90\%$ observed specificity as shown in [Table 9](#).

Table 9: Individual Reader Results for Specificity

	Primary Efficacy Cohort (N = 47)	
	Read negative/ Presumed negative	%
Median	47/47	100%
Reader 1	47/47	100%
Reader 2	46/47	98%
Reader 3	47/47	100%
All Reads	140/141	99%

In addition, 14 subjects who were found to be amyloid positive at autopsy (CERAD diagnosis >2, moderate or frequent plaques) were included among the 40 positive control cases evaluated in the specificity read. The majority result of the blinded readers for all of the 14 cases was A β + (100% sensitivity). One reader scored all 14 cases A β +, and the other two readers each scored 13/14 cases A β + (93%).

5.2.2. Phase III AV-45-A07 Conclusions

Both Phase III primary analysis objectives were met. All secondary endpoints (tests of correlation between regional PET measures and regional measures of amyloid pathology) also were met, and showed strong statistically significant Spearman's rho (ρ) correlations. Moreover, all prospectively-defined exploratory analyses demonstrated positive results. The magnitude, statistical significance, and consistency of results provide strong support for the proposed indication for the following reasons:

- The pivotal trial included two independent primary analysis endpoints involving two separate populations.
- Statistically significant results were obtained in both primary analyses (i.e., the correlation analysis and specificity analysis). The primary correlation analysis between the ordinal rating of β -amyloid levels on an independent read of the florbetapir-PET scans and the cortical β -amyloid levels at autopsy, as assessed by IHC in the Autopsy Cohort, was strong ($\rho = 0.78$), and statistically significant ($P < 0.0001$), and exceeded the value required to confirm the hypothesis.
- For the Specificity Cohort, the results also exceeded the target with an observed specificity of 100% (95% CI: 91-100%).
- The primary results were supported by multiple prospectively-defined secondary and exploratory endpoints in this study. Statistically significant correlations were found for every comparison between PET imaging and autopsy results for β -amyloid. Similar results were also obtained when visual ratings of amyloid levels in individual cortical regions were compared with regional IHC measurements at autopsy. In addition, statistically-significant correlations of florbetapir-PET image measurements were observed versus the neuropathology-standard method of silver staining and neuritic plaque CERAD score determination.

- All primary and secondary endpoints were met not only for the median/majority read (as was prespecified) but also by each of the three readers.

5.2.3. Phase II AV-45-A05 Study

The AV-45-A05 Phase II study was a prospectively designed study to evaluate amyloid-PET imaging in cognitively normal subjects, subjects with a clinical diagnosis of AD, and subjects with MCI.

Objective

The primary objective of AV-45-A05 was to differentiate healthy controls from subjects with a clinical diagnosis of AD or MCI and determine the relationship between florbetapir F18 images and clinical/epidemiological risk factors for brain amyloid pathology.

Population

The AD subjects were at least 50 years old, with probable AD (NINCDS-ADRDA criteria), and an MMSE score between 10 and 24. MCI subjects were presenting for initial diagnosis of cognitive impairment or had presented for initial diagnosis of cognitive impairment within the past year, were at least 50 years old, had complaint of memory or cognitive decline corroborated by an informant, a clinical dementia rating (CDR) of 0.5, MMSE > 24 and no obvious causes for the impairment. The HC subjects were distributed across age deciles of 50 to 59, 60 to 69, 70 to 79, and ≥ 80 years, had an MMSE score ≥ 29, and were cognitively normal based on history and psychometric test battery.

Image Evaluation Methods

For all subjects, the PET images were evaluated visually using semi-quantitative (0-4) and qualitative ratings (Aβ+, Aβ-). The image evaluation methods were similar to those described above for Study A07.

All images were also evaluated quantitatively by calculation of the cortical SUVR (see A07 Imaging Analysis Methods above). Briefly, the SUVR is calculated as the mean of the ratios of the florbetapir uptake in 6 cortical regions (frontal, anterior cingulate, temporal, parietal, posterior cingulate and precuneus) divided by the uptake in the whole cerebellum. The SUVR is used to represent a quantitative measure of brain florbetapir retention.

Results

Demographics and Baseline

Study A05 Demographics and selected baseline characteristics are summarized in [Table 10](#).

Table 10: A05 Study Demographic and Baseline Characteristics

Clinical Diagnostic Group	AD (n=45)	MCI (n=60)	HC (n=79)	Total (N=184)
Age (years)				
No.	45	60	79	184
Mean (SD)	75.4 (9.21)	71.7 (10.23)	69.4 (11.04)	71.6 (10.57)
Median	78.0	73.0	70.0	74.0
Minimum, maximum	52, 88	50, 90	50, 92	50, 92
Age category, No. (%)				
50-59 years	5 (11.1%)	7 (11.7%)	19 (24.1%)	31 (16.8%)
60-69 years	6 (13.3%)	17 (28.3%)	19 (24.1%)	42 (22.8%)
70-79 years	19 (42.2%)	24 (40.0%)	21 (26.6%)	64 (34.8%)
≥80 years	15 (33.3%)	12 (20.0%)	20 (25.3%)	47 (25.5%)
Gender, No. (%)				
Male	26 (57.8%)	27 (45.0%)	34 (43.0%)	87 (47.3%)
Female	19 (42.2%)	33 (55.0%)	45 (57.0%)	97 (52.7%)
Race, No. (%)				
Asian	0	0	1 (1.3%)	1 (0.5%)
Black or African-American	1 (2.2%)	2 (3.3%)	4 (5.1%)	7 (3.8%)
Caucasian	41 (91.1%)	58 (96.7%)	72 (91.1%)	171 (92.9%)
Native American/Alaskan Native	0	0	0	0
Other	3 (6.7%)	0	2 (2.5%)	5 (2.7%)
11-item ADAS Cognitive Subscale				
No.	45	60	79	184
Mean (SD)	22.0 (9.80)	9.5 (5.02)	4.7 (2.41)	10.5 (9.03)
Mini-Mental State Examination				
No.	45	60	79	184
Mean (SD)	20.6 (3.85)	27.4 (1.78)	29.5 (0.50)	26.6 (4.18)
Wechsler Logical Memory Scale I Story A (Immediate Recall)				
No.	45	60	79	184
Mean (SD)	3.9 (3.74)	10.5 (3.87)	13.8 (3.18)	10.3 (5.28)
Wechsler Logical Memory Scale II Story A (Delayed Recall)				
No.	45	60	79	184
Mean (SD)	1.5 (2.77)	8.6 (4.59)	12.6 (3.77)	8.6 (5.82)

Abbreviations: AD: Alzheimer's disease; HC: cognitively normal (healthy) controls; MCI: mild cognitive impairment

Note: Percentages are based on the number of subjects in each clinical diagnostic group.

Efficacy Results

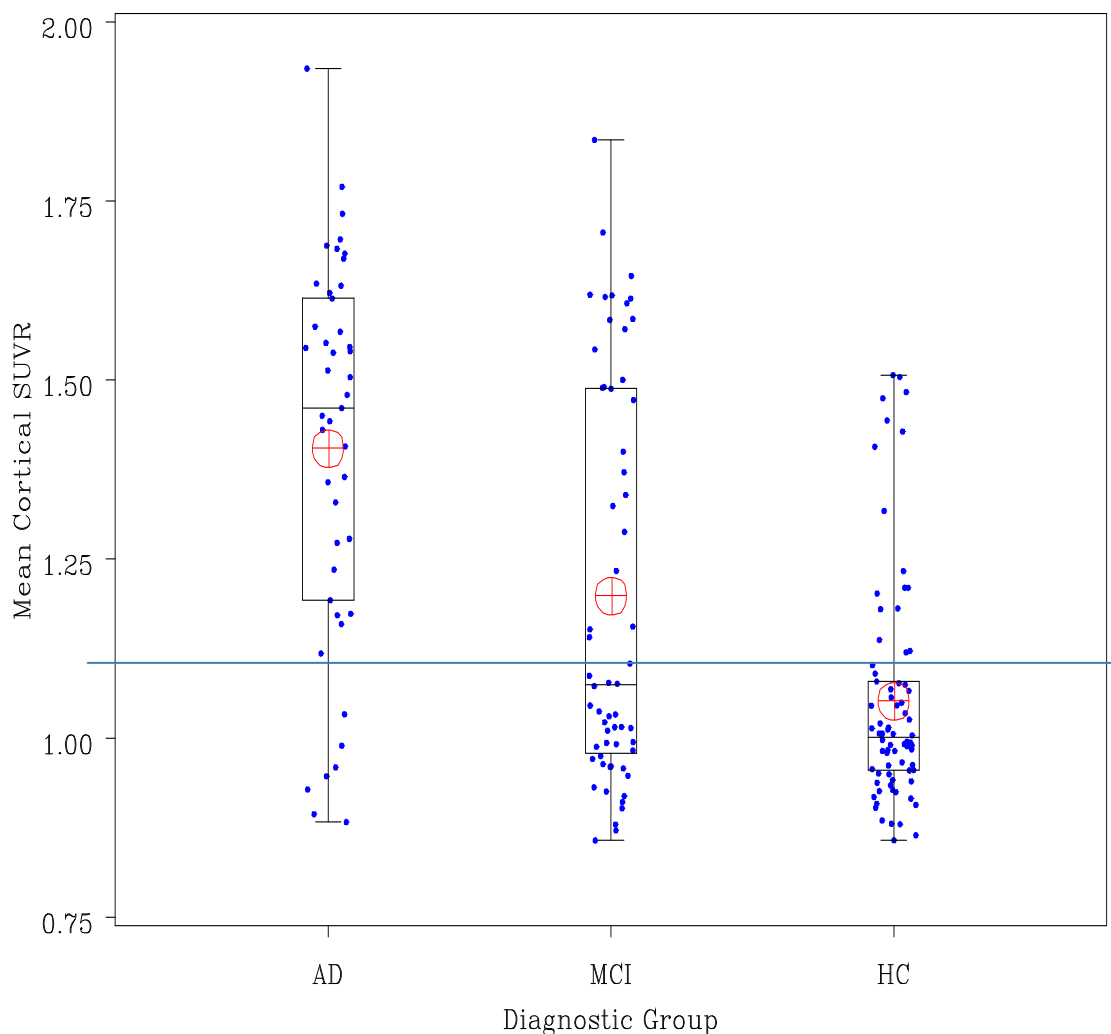
The florbetapir results described below demonstrate the relationship between florbetapir F18 images and clinical/epidemiological risk factors for brain amyloid pathology that are consistent with the results that have been reported in the autopsy literature^{13,14,15,16,17} and also consistent with findings from other PET amyloid tracers.^{18,19}

Clinical Presentation

The florbetapir-PET cortical brain signal was highest in subjects with AD, lowest in HC, and intermediate in subjects with MCI (see [Figure 3](#)). All differences between diagnostic groups were statistically significant regardless of whether florbetapir-PET signal was measured quantitatively (SUVR), or by blinded semi-quantitative or qualitative visual image reading. Of the subjects with a clinical presentation of AD, 75.6% were β -amyloid positive ($A\beta+$) by the blinded reader rating of the PET scan; while 38.3% of subjects with MCI were $A\beta+$ by PET and 14.1% of HC subjects were rated as $A\beta+$.

The observation that 24% of clinically diagnosed probable AD subjects were negative for amyloid closely matches the expected rate of false-positive clinical diagnosis of AD based on autopsy literature (Lim et al ²⁰ reported that 20% of clinical diagnosed AD subjects did not have AD at autopsy and lacked amyloid pathology; and Pearl et al ¹⁴ reported that 23% of clinically diagnosed AD subjects did not have AD at autopsy and lacked amyloid pathology). Similarly, the observation that 40% of MCI subjects were amyloid positive by florbetapir-PET scan is consistent with the autopsy literature that shows 33% to 62% of MCI subjects are amyloid positive at postmortem examination.^{21,22}

Figure 3: Mean Cortical Standardized Uptake Value Ratios Box Plots by Clinical Diagnostic Group – A05 Efficacy Population

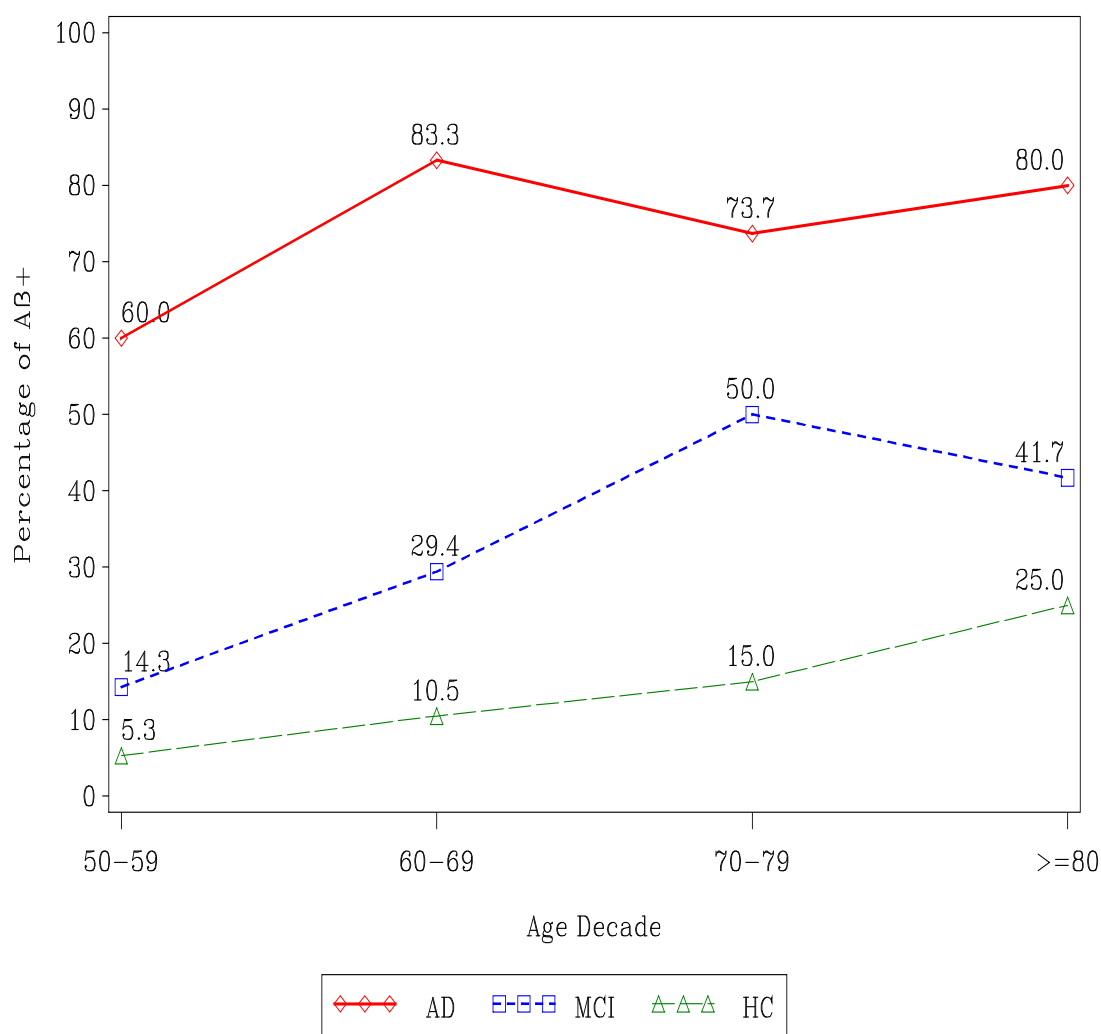


Note: Individual data points are displayed with a dot and equivalent values are offset. The mean for each clinical diagnostic group is indicated by the circled plus sign, and the median is indicated by the horizontal line. The blue line indicates the 1.10 threshold for positivity (as defined in study A03).

Age

In HC subjects, the percentage of subjects rated A β + increased with age from 5.3% to 10.5%, 15.0%, and 25.0% of subjects at ages 50 to 59, 60 to 69, 70 to 79, and 80 years or more, respectively (See Figure 4). The increased proportion of HC rated positive for β -amyloid is consistent with reported autopsy literature results in cognitively normal subjects.¹³

Figure 4: Qualitative Assessment of Images by Age Decade - Efficacy Population



Note: Percentages are based on the number of subjects in each clinical diagnostic group within each age decade.

ApoE genotype

The ApoE ϵ 4 allele is the largest known genetic risk factor for AD (excluding the dominantly inherited mutations for AD). Although ApoE genotype cannot be considered synonymous with brain β -amyloid, the A05 analyses indicate that the florbetapir-PET signal is consistent with the increased risk of amyloid pathology for those with the ApoE ϵ 4 allele.

None of the subjects in the ApoE ϵ 2 group were rated as A β +, regardless of clinical diagnostic group. The ApoE ϵ 4 group had a higher proportion of subjects rated A β +, than the ApoE ϵ 3 group (see [Table 11](#)).

Using quantitative analysis, subjects in the ApoE ϵ 2 group had significantly lower mean cortical SUVR than subjects in the ApoE ϵ 4 group, regardless of diagnostic category.

Table 11: Qualitative Assessment of Images by ApoE Group - Efficacy Population

Clinical Diagnostic Group	AD (n=45)	MCI (n=60)	HC (n=78)	Total (N=183)
ApoE2				
No.	2	4	12	18
A β +, No. (%)	0	0	0	0
A β -, No. (%)	2 (100.0%)	4 (100.0%)	12 (100.0%)	18 (100.0%)
ApoE3				
No.	17	29	44	90
A β +, No. (%)	10 (58.8%)	4 (13.8%)	7 (15.9%)	21 (23.3%)
A β -, No. (%)	7 (41.2%)	25 (86.2%)	37 (84.1%)	69 (76.7%)
ApoE4				
No.	21	22	16	59
A β +, No. (%)	19 (90.5%)	16 (72.7%)	3 (18.8%)	38 (64.4%)
A β -, No. (%)	2 (9.5%)	6 (27.3%)	13 (81.3%)	21 (35.6%)
ApoE genotype missing				
No.	5	5	6	16
A β +, No. (%)	5 (100.0%)	3 (60.0%)	1 (16.7%)	9 (56.3%)
A β -, No. (%)	0	2 (40.0%)	5 (83.3%)	7 (43.8%)

Note: Percentages are based on the number of subjects in each clinical diagnostic group within each ApoE group. ApoE2 = ϵ 2 and ϵ 3 genotype, ApoE3 = ϵ 3 and ϵ 3 genotype, and ApoE4 = ϵ 3 and ϵ 4 genotype or ϵ 4 and ϵ 4 genotype.

Cognitive testing

Across all clinical presentation groups, subjects with high florbetapir-PET signal performed worse than subjects with low florbetapir-PET signal on all memory and cognitive tests, regardless of whether florbetapir-PET signal was measured quantitatively, semi-quantitatively, or qualitatively. For cognitively normal subjects, mean cortical SUVR was correlated with scores on the Wechsler Logical Memory I Story A (immediate paragraph recall) ($P=0.0016$), Wechsler Logical Memory II Story A (delayed paragraph recall) ($P=0.0135$), Digit-Symbol Substitution ($P=0.0173$), ADCS ADL Scale ($P=0.0386$), and the 11-item ADAS cognitive subscale ($P=0.0052$). In each case, increasing amyloid burden, as measured by SUVR, correlated with poorer cognitive performance.

A stepwise multivariate model, with age, years of education, presence or absence of an ApoE4 allele, and SUVR as initial factors, further supported the relationship between florbetapir-PET amyloid signal and cognitive performance. Within the cognitively normal group, mean cortical SUVR was statistically significantly related to Wechsler Logical Memory I Story A (immediate paragraph recall) ($P=0.0060$) and II Story A (delayed paragraph recall) ($P=0.0470$), with trends that approached, but did not reach, significance on the ADCS ADL Scale ($P=0.0812$), and the 11-item ADAS cognitive subscale ($P=0.0600$). The presence of significant amyloid burden as

measured by SUVR was a better predictor of poorer cognitive performance than any other variable, including age and ApoE genotype.

Similar results were obtained when scans were evaluated by the blinded readers using the qualitative (positive/negative) binary scale visual interpretation. Within the cognitively normal group, subjects rated as A β ⁺ had statistically significantly poorer scores on the Wechsler Logical Memory I Story A (immediate paragraph recall) (P=0.0200) and II Story A (delayed paragraph recall) (P=0.0305), on Digit-Symbol Substitution (P=0.0080), on the ADCS ADL Scale (P=0.0321), and on the 11-item ADAS cognitive subscale (P=0.0260) than subjects rated as A β ⁻.

Overall these results support the hypothesis that florbetapir-PET detects a pathologically significant level of amyloid accumulation.

5.2.4. Phase II AV-45-A05 Conclusions

The results of the Phase II AV-45-A05 study provided strong supportive evidence of the effectiveness of florbetapir-PET for the proposed indication of imaging brain β -amyloid aggregates in a cross-sectional study of AD, MCI and cognitively normal subjects, as might be experienced in routine clinical use. The florbetapir-PET signal varied as a function of factors known to be related to levels of brain amyloid pathology (clinical diagnosis, age, and ApoE genotype). In addition, the study showed that a high florbetapir-PET cortical brain signal correlated with poorer cognitive performance in cognitively normal elderly control subjects, suggesting that accumulation of β -amyloid in the brain may be pathological even in apparently cognitively normal subjects.

5.2.5. Integrated Clinical Results in Support of Autopsy Correlation

The pivotal A07 trial was the only study which directly compared florbetapir-PET measures of β -amyloid to post-mortem pathological measures of β -amyloid. However, other findings from the NDA integrated dataset provide supportive information for the effectiveness of florbetapir-PET in detecting pathologically significant β -amyloid in the living human brain. Specifically, the relationship between florbetapir-PET and clinical/epidemiological risk factors or correlates of amyloid burden such as clinical diagnosis presentation, age group, ApoE status, and cognitive performance were integrated across all of the development trials and evaluated.

Specificity, the second primary measure of effectiveness of florbetapir-PET in the A07 pivotal trial, was also evaluated in the integrated clinical data set across multiple trials.

Population

The analysis of integrated efficacy included subject data from the completed studies of florbetapir F 18. The only data types excluded were the following:

- Data that were duplicative in nature, arising from either second acquisitions from the same subject or second evaluations of the same scan.
- Cognitive scales from autopsy subjects in Study A07 (their concomitant illnesses and medications for end-of-life illnesses alter the reliability of the cognitive measures)

In total, there are 474 subjects in the integrated analysis of florbetapir efficacy.

Results

Demographics

Demographic data and baseline characteristics for the subjects across the 6 efficacy studies are provided in [Table 12](#).

For the purposes of analysis, subjects were characterized as Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), Other Dementing Disorder (ODD), older cognitively healthy controls (OHC), or young cognitively healthy controls (YHC). Similar standardized entry/classification criteria were used across trials, except for the Autopsy Cohort of Study A07 in which the preexisting clinical characterization was accepted, and a brief cognitive battery was used to validate the clinical diagnosis at the time of enrollment.

Table 12: Demographics data—Integrated Efficacy Population

Parameter	Diagnostic Presentation Group					Overall (N = 474)
	AD (N = 133)	MCI (N = 85)	ODD (N = 21)	OHC (N = 146)	YHC (N = 89)	
Sex, No. (%)						
Male	58 (43.6%)	45 (52.9%)	7 (33.3%)	73 (50.0%)	60 (67.4%)	243 (51.3%)
Female	75 (56.4%)	40 (47.1%)	14 (66.7%)	73 (50.0%)	29 (32.6%)	231 (48.7%)
Age, years						
No.	133	85	21	146	89	474
Mean (SD)	77.4 (9.95)	73.4 (11.58)	79.9 (11.62)	70.8 (13.37)	29.2 (8.25)	65.7 (21.02)
Median	79.0	74.0	79.0	68.5	28.0	71.0
Min, Max	52, 102	47, 94	57, 104	50, 99	18, 48	18, 104
Age Category, No. (%)						
≥ 65	118 (88.7%)	65 (76.5%)	19 (90.5%)	92 (63.0%)	0	294 (62.0%)
< 65	15 (11.3%)	20 (23.5%)	2 (9.5%)	54 (37.0%)	89 (100.0%)	180 (38.0%)
Age Category by Decade, No. (%)						
< 50	0	1 (1.2%)	0	0	89 (100.0%)	90 (19.0%)
50 – 59	11 (8.3%)	11 (12.9%)	1 (4.8%)	36 (24.7%)	0	59 (12.4%)
60 – 69	17 (12.8%)	20 (23.5%)	3 (14.3%)	38 (26.0%)	0	78 (16.5%)
70 – 79	48 (36.1%)	28 (32.9%)	7 (33.3%)	25 (17.1%)	0	108 (22.8%)
≥ 80	57 (42.9%)	25 (29.4%)	10 (47.6%)	47 (32.2%)	0	139 (29.3%)
Race, No. (%)						
White	123 (92.5%)	79 (92.9%)	17 (81.0%)	128 (87.7%)	66 (74.2%)	413 (87.1%)
Non-white	10 (7.5%)	6 (7.1%)	4 (19.0%)	18 (12.3%)	23 (25.8%)	61 (12.9%)
ApoE Group, No. (%) ^a						
Apoe2	5 (4.4%)	9 (10.6%)	1 (4.8%)	15 (11.9%)	10 (12.0%)	40 (9.3%)
Apoe3	38 (33.6%)	39 (45.9%)	1 (4.8%)	67 (53.2%)	43 (51.8%)	188 (43.9%)
Apoe4	48 (42.5%)	26 (30.6%)	12 (57.1%)	20 (15.9%)	25 (30.1%)	131 (30.6%)
Missing	22 (19.5%)	11 (12.9%)	7 (33.3%)	24 (19.0%)	5 (6.0%)	69 (16.1%)

Parameter	Diagnostic Presentation Group					Overall (N = 474)
	AD (N = 133)	MCI (N = 85)	ODD (N = 21)	OHC (N = 146)	YHC (N = 89)	
Time from Symptoms Onset, months						
No.	132	81	19	—	—	232
Mean (SD)	81.2 (52.11)	32.1 (22.41)	72.2 (52.43)	—	—	63.3 (49.59)
Median	69.5	29.0	64.0	—	—	54.0
Min, Max	7, 384	1, 114	22, 239	—	—	1, 384
Time from Disease Diagnosis, months						
No.	133	85	20	—	—	238
Mean (SD)	52.5 (47.89)	8.1 (15.98)	45.9 (51.14)	—	—	36.1 (44.93)
Median	44.0	1.0	27.0	—	—	20.0
Min, Max	0, 359	-3, 73	6, 239	—	—	-3, 359
MMSE, No. ^b						
No.	79	60	—	102	86	327
Mean (SD)	19.9 (4.16)	27.4 (1.78)	—	29.6 (0.49)	29.7 (0.56)	26.9 (4.59)
Median	21.0	27.0	—	30.0	30.0	29.0
Min, Max	10, 24	24, 30	—	29, 30	27, 30	10, 30

^a ApoE genotype data were collected from A04, A05, and A07 studies only. Calculation of percentage was based on data availability and using total number of subjects potentially having measurements as its denominator.

^b Cognitive assessments from subjects of the A07 autopsy cohort were excluded from the summary.

The enrolled populations for the 6 efficacy studies in the NDA fully encompass the patient population expected to undergo florbetapir-PET imaging when it is marketed, including subjects with mild to severe memory deficits attributable to both AD and other dementias. In addition to presentation of illness, the enrolled population encompasses the age range of the expected population.

The AD group tended to be older than the OHC group on average because an effort was made to study healthy control subjects in each decade after 50 years of age to understand the effects of age on amyloid accumulation in cognitively healthy subjects. Nonetheless, the number of healthy control subjects > 65 years of age was roughly comparable to the number of AD subjects > 65 years that were imaged in these studies. AD and ODD subjects also tended to be lighter and have lower BMIs than other groups, perhaps reflecting poorer nutrition as a result of their impairments. The AD and the ODD group also had a higher proportion of subjects with the ApoE ε4 allele than was seen in the other presentation groups. Except for those factors that were determined by study design (population age and cognitive status), there were no major differences in populations across the studies.

High Specificity of Florbetapir-PET

In the combined efficacy dataset there were 90 subjects who were expected to have no brain β-amyloid and had florbetapir PET scans evaluated for the presence or absence for β-amyloid. All 90 florbetapir PET scans were evaluated as being negative for β-amyloid by the majority of the blinded readers, yielding an estimate of 100% specificity on the integrated data set. In addition, there were 16 of 35 subjects who had an autopsy that had negligible, or < sparse plaques as amyloid pathology. These data are summarized in [Table 13](#).

Table 13: Specificity Across Florbetapir Studies

Study	Subjects (YHC or Confirmed A β -)	Number (%) Evaluated as Negative on Florbetapir Scan		
		Qualitative Reads (A β -)	Semiquantitative Ratings (0 or 1)	Quantitative SUVR < 1.10
A03	6	6 (100%)	6 (100%)	6 (100%)
A04	7	7 (100%)	7 (100%)	7 (100%)
A07 Specificity ^a	74	74 (100%) ^a	—	74 (100%)
A07 Autopsy Cohort (YHC, No autopsy) ^b	3	—	3 (100%)	3 (100%)
A07 Autopsy ^c (No AD at Autopsy)	16	—	16 (100%)	16 (100%)
Total subjects across studies	106	87 (100%)	32 (100%)	106 (100%)

^a Note that of the 74 subjects enrolled in Specificity Cohort, one subject was older than 50 years (due to protocol violation) and thus was not counted as YHC in other integrated tables sorted by age. However, this subject was included in this table as it was sorted by study.

^b Three subjects in the Autopsy Cohort did not come to autopsy but were < 50 years old.

^c Of the 35 subjects that came to autopsy, 16 were found to have no AD and nonsignificant levels of β -amyloid at autopsy.

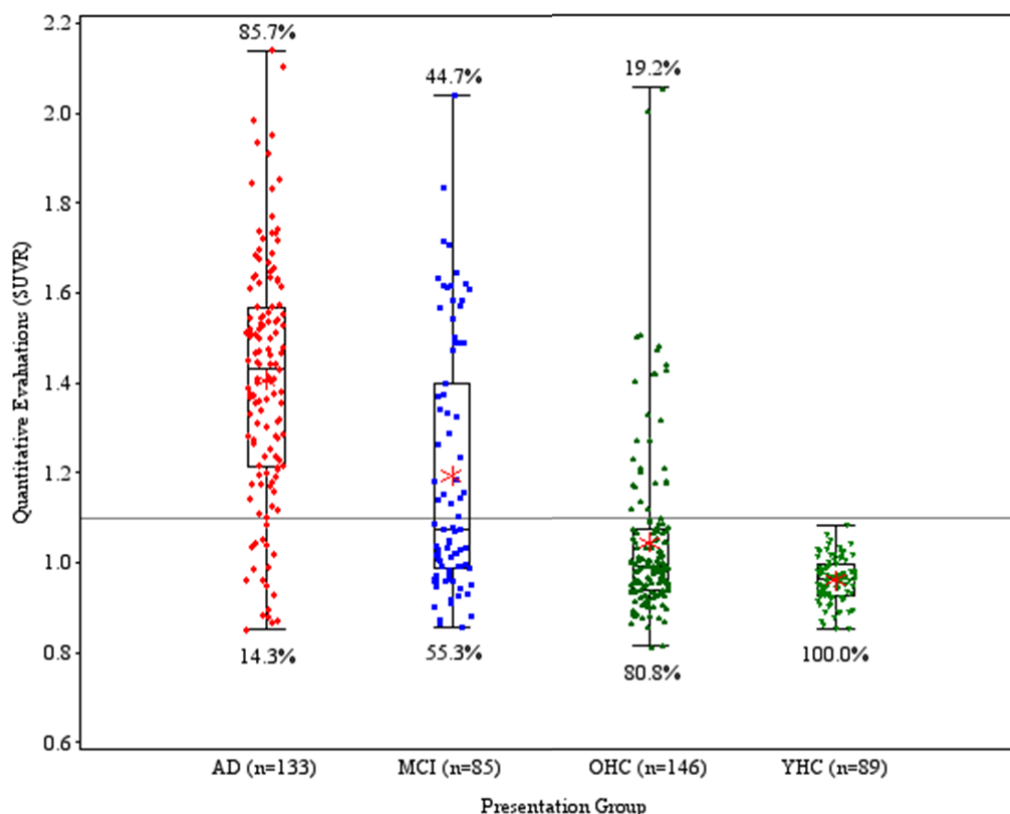
Florbetapir-PET and Factors Known to Influence β -amyloid Deposition

The integrated florbetapir results briefly discussed below further support the conclusions discussed in Clinical Study A05 above. The integrated results further demonstrate the relationship between Florbetapir F18 images and clinical/epidemiological risk factors for brain amyloid pathology in living subjects.

1. Relationship Between Clinical Presentation and florbetapir-PET Amyloid Burden:

Florbetapir-PET image evaluation by presentation group shows that the signal (and proportion of subjects rated positive) was highest in subjects with AD, lowest in HC, and intermediate in subjects with MCI and ODD. These pooled analyses indicate that the florbetapir PET signal strongly follows the expected distribution of β -amyloid across clinical diagnostic groups.

Figure 5: Distribution of Quantitative SUVR Values by Presentation Group



“*” represents the mean, the “-” signifies the median, the outer boundaries indicate the range, and the box indicates the quartiles (75% and 25%). The numerical percent given below each distribution represents the total percent of subjects that were below the threshold for a positive scan (< 1.10).

2. Relationship between age and florbetapir-PET amyloid burden:

The integrated analysis demonstrated a positive association between age and levels of β -amyloid by florbetapir-PET. In the HC group, mean SUVR was seen to increase with age. When bisected into geriatric and nongeriatric subpopulations, the ≥ 65 group had a higher mean SUVR than the < 65 group ($P < 0.0001$). This increase in SUVR is not due to an increase in each member of the group but is rather due to an increasing proportion of subjects with positive florbetapir studies. In contrast, in the AD group there was no statistically significant increase in amyloid levels with age. This is expected since AD subjects, in accordance with established neuropathological criteria, should have pathologically-significant levels of β -amyloid regardless of age.

Relatively few MCI subjects under the age of 60 showed elevated amyloid, suggesting an alternative etiology for cognitive impairment is more common than AD in this age group (mild cognitive impairment of non-neurodegenerative etiology rather than prodromal AD). These analyses show that the pooled data set continues to support the findings of individual studies. Overall, these results are consistent with age-related trends in pathological β -amyloid detection reported in autopsy studies of cognitively normal elderly subjects and patients with AD. ^{13,14,15,16,17}

3. Relationship between ApoE and florbetapir-PET amyloid burden:

ApoE ϵ 4 was highly associated with increased β -amyloid on florbetapir-PET scans across multiple presentation groups. For the MCI and AD groups, the presence of ApoE4 alleles was strongly associated with a positive florbetapir-PET scan by qualitative evaluation (see Table 14). The ApoE ϵ 4 allele is the largest known genetic risk factor for AD (excluding the dominantly inherited mutations for AD). Although ApoE genotype cannot be considered synonymous with β -amyloid, the pooled analyses indicated that the florbetapir-PET signal is consistent with the increased risk of amyloid pathology of ApoE ϵ 4 and is even sensitive to detect the reduced risk associated with ApoE ϵ 2 allele.

Table 14: Relationship of ApoE4 Allele to Rate of Having a Positive Florbetapir-PET Scan in the ISE Data Set by Presentation Group

Parameter	Statistics	AD		MCI		OHC	
		ApoE4 (N = 48)	Non-ApoE4 (N = 43)	ApoE4 (N = 26)	Non-ApoE4 (N = 48)	ApoE4 (N = 20)	Non-ApoE4 (N = 82)
Qualitative Interpretations							
Aβ+	n (%)	25 (92.6%)	14 (56.0%)	16 (72.7%)	4 (12.1%)	3 (17.6%)	7 (12.1%)
Aβ−	n (%)	2 (7.4%)	11 (44.0%)	6 (27.3%)	29 (87.9%)	14 (82.4%)	51 (87.9%)
P value ^a		0.0034	—	< 0.0001	—	0.6855	—

Abbreviations: AD, Alzheimer's disease, MCI, mild cognitive impairment, OHC, older healthy controls.

^a *P* value is from a Fisher exact test comparing the proportion of A β + subjects within each presentation group.

Notes:

1. Qualitative interpretations were not collected from subjects in the Study A07 Autopsy Cohort
2. Percentage is calculated using total number of subjects with A β + and A β - as denominator.
3. Qualitative interpretation is the majority of blinded reads.

4. Relationship between cognition and florbetapir-PET amyloid burden:

When all presentation groups are combined, β -amyloid levels measured with florbetapir-PET were associated with poorer cognitive and memory performance.

When the relationship between cognitive performance and amyloid burden was examined by presentation groups, there remained several strong associations between increased amyloid burden and poorer cognition, most prominently in the cognitively OHC population. The OHC population showed significant positive correlations between SUVR and ADAS ($P = 0.006$) and inverse correlations with the memory performance tests, WLM-I ($P = 0.0005$) and WLM-II ($P = 0.0192$).

OHC subjects with a florbetapir-PET rated positive for β -amyloid also had statistically worse cognition on the ADAS ($P = 0.0071$) and memory (WLM-I and WLM-II tests: $P = 0.0442$ and $P = 0.0290$, respectively).

Notably, there was no significant correlation seen in the MCI group between florbetapir-PET signal and memory performance. The most likely reason is that while the MCI group is, by definition, comprised of subjects who are all impaired cognitively, the etiology of these cognitive impairments are varied. Typically, less than half of MCI patients go on to develop AD (and less than half of the MCI group was positive for β -amyloid pathology by florbetapir

PET scan). Given that much of the cognitive impairment in the MCI group is not due to β -amyloid pathology, it is not surprising that the correlations with the florbetapir-PET signal would be weaker.

Overall, the strong inverse associations between brain amyloid levels and cognitive performance in the OHC, support the efficacy for florbetapir-PET to detect β -amyloid pathology. Furthermore, the ability to detect these correlations in otherwise healthy subjects implies florbetapir-PET may be detecting a very early but clinically relevant pathology.

5.2.6. Integrated Efficacy Results: Conclusion

Integrated efficacy results from the NDA trials of florbetapir-PET have indicated that both visual and semi-automated quantitation of florbetapir-PET scans (i.e. SUVR) correlated in the expected manner with parameters known to be associated with increased prevalence of underlying β -amyloid pathology, including: 1) disease diagnostic status (eg, AD versus HC), 2) age, 3) ApoE genotype, and 4) cognitive performance.

In summary, the magnitude, statistical significance, and consistency of the results obtained during the pivotal trial as well as across all clinical efficacy trials meet the standard of providing substantial evidence from adequate and well-controlled investigations demonstrating the effectiveness of florbetapir-PET for the detection, or exclusion, of pathologically significant levels of β -amyloid aggregates in the brain by PET.

5.2.7. Nonclinical Studies supporting Efficacy

Nonclinical studies support the conclusion that florbetapir F 18 binds with high selectivity and specificity to β -amyloid aggregates and that the binding intensity of florbetapir F 18 is quantitatively correlated with the density of β -amyloid aggregates quantified by standard neuropathological techniques.

Objective

To determine the correlation between in vitro florbetapir F 18 binding in human brain tissue and β -amyloid levels measured by standard neuropathological analysis and to characterize the binding affinity (K_d) and density (B_{max}).

Methods

Autoradiography assessment was performed by incubating AD and HC brain tissue with florbetapir F18 followed by exposure to film. After the film was developed, the images were digitized. The optical density (OD) of the florbetapir signal was determined for the gray matter areas.

For all tissue, β -amyloid burden was quantified using traditional neuropathological staining procedures, including Bielschowsky silver staining, thioflavin S staining, and immunohistochemistry.

Competitive binding assays using gray matter homogenates from brain samples of Alzheimer's Disease subjects were used to determine the K_d and B_{max} values.

Results

The dissociation constant for florbetapir F 18 was measured as $K_d = 3.7 \pm 0.3$ nM in homogenates of human AD brain tissue. The binding of florbetapir F 18 to β -amyloid aggregates was directly visualized in brain sections from subjects with AD pathology using autoradiography and matched against histopathological measures of β -amyloid or neuritic plaque count. There was no florbetapir signal in brain tissue sections from HC subjects. All studies demonstrated strong and statistically significant correlations between in vitro florbetapir F 18 binding and β -amyloid aggregate deposition (Table 15 and Figure 6).

The autoradiography studies also established the selectivity of florbetapir F 18 binding to β -amyloid aggregates versus other pathological deposits in the human brain. Florbetapir F 18 did not bind to tissue sections from subjects with neurofibrillary tangle (tau) pathology. In subjects with mixed β -amyloid plaque and neurofibrillary tangle pathology, the binding of florbetapir F 18 was strongly correlated with plaque, but not tangle, density. The selectivity of florbetapir F 18 binding to β -amyloid was further established by testing its binding to a battery of known receptors and ion channels. These studies did not reveal any binding to other receptors up to concentrations 1000-times higher than the K_d value of florbetapir F 18.

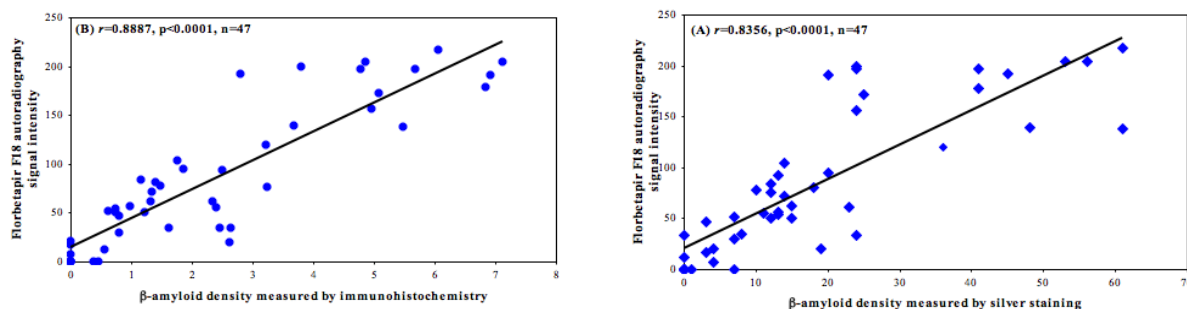
Table 15: Correlation Coefficients and P Values of β -Amyloid Density in Postmortem Human Brain Tissue

<u>Correlation</u>	r	p
Florbetapir F 18 ARG vs amyloid plaque score (silver stain)	0.84	< 0.0001
Florbetapir F 18 ARG vs amyloid plaque score (thioflavin S)	0.73	< 0.0001
Florbetapir F 18 ARG vs tangles score (silver stain)	0.23	0.11
Florbetapir F 18 ARG vs β -amyloid density (IHC)	0.89	< 0.0001

Abbreviations: ARG, autoradiography (quantified by measuring optical density); IHC, immunohistochemistry.

Figure 6: Correlation of Florbetapir F 18 Autoradiography Signal Intensity (Optical Density) with (left) β -Amyloid Aggregate Deposition Measured by

Immunohistochemical Staining and (right) Amyloid Plaque Counts in Silver Staining



5.2.8. Nonclinical Efficacy Conclusions

The data obtained in the nonclinical studies support the following conclusions:

1. Florbetapir F 18 selectively binds to and labels β -amyloid aggregates in post-mortem human brain tissue.
2. The binding intensity of florbetapir F 18 is quantitatively correlated with the density of β -amyloid aggregates quantified by standard neuropathological techniques.

5.3. Efficacy Conclusions

The focus of the florbetapir F 18 clinical development program was to establish the relationship between amyloid burden, as evidenced on the florbetapir-PET image, and the underlying true amyloid pathology in the subjects or cohort under evaluation. Four lines of evidence have been presented which support the effectiveness of florbetapir-PET for imaging β -amyloid pathology in the human brain:

- **Florbetapir-PET signal correlates to amyloid histopathology present at autopsy.** The pivotal trial, Study ^{18}F -AV-45-A07, demonstrated that there is a strong, statistically significant correlation between the level of cortical tracer uptake in the PET image and amyloid burden at autopsy.
- **Florbetapir-PET scans are negative in subjects without amyloid pathology.** The pivotal Phase III trial also demonstrated the high specificity of florbetapir-PET in subjects devoid of brain β -amyloid pathology (the Specificity Cohort). The majority visual binary read resulted in 100% (47 of 47) of scans read as amyloid negative ($\text{A}\beta^-$). In individual blinded reads, the specificity was 100% for two readers and 98% for one reader. Importantly, the majority blinded reader result demonstrated amyloid-positive PET scans in 14/14 (100%) of autopsy subjects which were included as positive controls in the specificity blinded read and had pathologically significant (CERAD moderate/frequent) levels of β -amyloid plaque at autopsy.
- **Florbetapir-PET results correlate with known clinical/epidemiological risk factors for brain amyloid.** Phase I and II trials have shown that the florbetapir-PET signal

correlates factors known to be associated with increased prevalence of underlying β -amyloid pathology such as clinical diagnosis, age, ApoE genotype, and cognitive performance. Specifically, rates of amyloid positivity measured by florbetapir-PET varied as follows:

- AD > MCI > HC
 - older > younger controls
 - ApoE4 carriers > ApoE3/3 carriers > ApoE2 carriers
 - A β + HC show worse cognitive performance than A β - HC.
- **Florbetapir F 18 binds avidly and specifically to brain amyloid in vitro and ex vivo.** Nonclinical studies using tissue derived from AD patients, cognitively normal elderly subjects, and patients with other neurodegenerative diseases, provided further supportive data that clearly demonstrated (1) florbetapir F 18 binds to aggregated β -amyloid with high affinity, (2) florbetapir-labeled amyloid plaques can be co-labeled with thioflavin, (3) the optical density of labeling on florbetapir F 18 autoradiography is strongly correlated with the amount of β -amyloid detected by quantitative ICH, and (4) florbetapir F 18 section labeling in human brain tissue is highly specific for β -amyloid pathology and is not seen in tissue from subjects with other neurological diseases without β -amyloid pathology.

5.4. Florbetapir Dosing and Acceptable Brain Imaging Timeframe

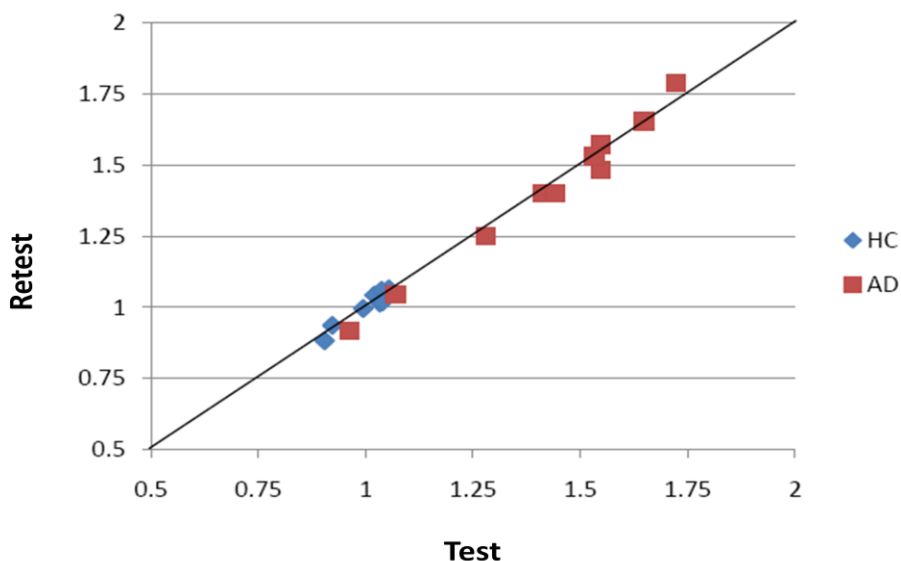
Study A03 was conducted in part to explore the range of effective doses for florbetapir F 18. Overall, visual ratings and quantitative SUVR assessments of beta-amyloid levels from the PET scans were similar for subjects given 111 MBq dose and 370 MBq florbetapir F 18. However, the subjective rating of image quality in the blinded image assessment was better at 370 MBq. Based on the better visual image quality rating and acceptable radiation dosimetry, a dose of 370 MBq was chosen as the standard dose for clinical application.

The pharmacodynamics of brain imaging in AD and HC subjects was also studied in this trial. Essentially equivalent separation was observed between the AD and HC groups in the cortical SUVR values obtained at any time between 30 and 90 minutes after injection of florbetapir F 18.

5.5. Florbetapir-PET Imaging Reliability

Study A04 evaluated the within-subject test–retest reliability of florbetapir-PET imaging. The florbetapir-PET scan was highly reproducible. A very high interclass correlation coefficient, or ICC (0.99), and low test–retest variability (< 5%) were observed for the quantitative image assessment (SUVR) as shown in Figure 7. Very good agreement ($\kappa > 0.85$) between test and retest scans was found on the visual read for both the qualitative (amyloid positive or amyloid negative) and semiquantitative (0 to 4) amyloid burden scores. A 10 minute scan was found to be adequate for high quality images and there are no statistical differences between quantitative analyses, including reproducibility, of a 10 minute scan or a 20 minute scan. Based on these results a scan time of 10 minutes is recommended for routine clinical application.

Figure 7: Test-Retest Reproducibility of SUVR



5.6. Florbetapir Safety

5.6.1. Clinical Safety

The integrated safety database for florbetapir F 18 contains 496 subjects who received 520 doses (24 subjects in study A04 received two doses) of florbetapir F 18 in 6 completed clinical studies conducted in the United States. Data including adverse event and serious adverse event reports, pre and post dose vital signs and laboratory investigations are available for all 496 subjects (safety population). In addition to these six completed studies, there are a number of ongoing studies that are using florbetapir F 18 as a biomarker, either in observational/longitudinal studies or in conjunction with investigational therapeutics. Serious adverse events collected from these ongoing studies are also included in the analyses below.

5.6.1.1. Adverse Events

In the Safety Population, 47 of 496 (9.5%) subjects experienced a total of 63 Treatment Emergent AEs (TEAEs), nearly all of which were assessed as mild or moderate in severity (62 of 63 AEs) and the majority assessed as not related (43 of 63 AEs) to the study drug. A summary of adverse events is provided in [Table 16](#) and [Table 17](#). The most frequently reported adverse events (in descending order of frequency) were headache (9 of 496 [1.8%]) subjects including 8 headache and 1 sinus headache), musculoskeletal pain (4 of 496 [0.8%] subjects), fatigue (3 of 496 [0.6%] subjects), and nausea (3 of 496 [0.6%] subjects). Analysis of the AEs by Study and by cognitive status did not reveal any clinically significant pattern. Cognitively impaired subjects showed no evidence for having increased rate of AEs. Study A02 had a higher rate of subjects with AEs (5 of 9 subjects) than the other studies, but nearly all of these were in the Musculoskeletal and Connective Tissue Disorders SOC and likely related to the lengthy scanning procedures (up to 6 hours) required to obtain biodistribution data for calculation of radiation dosimetry. Scanning protocols in the later Phase II and Phase III studies used only 10 minutes of

imaging and were completed within one hour after injection. These studies had a much lower rate of AEs in the Musculoskeletal and Connective Tissue Disorders SOC.

Table 16: Summary of Adverse Events by Subject Cognitive Status

	Safety Population		
	Cognitively Impaired (N = 247)	Cognitively Normal (N = 249)	Overall (N = 496)
Treatment-Emergent Adverse Events			
–Total no. of adverse events			
	24	39	63
–No. (%) of subjects with at least one adverse event			
	18 (7.3)	29 (11.6)	47 (9.5)
Treatment-Emergent Adverse Events by Severity			
–Total no. of adverse events			
Mild	13	31	44
Moderate	10	8	18
Severe	1	0	1
–No. (%) of subjects with at least one adverse event			
Mild	11 (4.5)	23 (9.2)	34 (6.9)
Moderate	6 (2.4)	6 (2.4)	12 (2.4)
Severe	1 (0.4)	0	1 (0.2)
Treatment-Emergent Adverse Events by Relationship to Study Drug			
–Total no. of adverse events			
Not related	17	26	43
Related	7	13	20
–No. (%) of subjects with at least one adverse event			
Not related	15 (6.1)	17 (6.8)	32 (6.5)
Related	3 (1.2)	12 (4.8)	15 (3.0)

Sources: Integrated Summary of Safety

Table 17: Adverse Events in descending order of frequency

Adverse Events Reported in More Than One Subject Who Received Florbetapir F 18 in Clinical Trials	
Adverse Event	
	N = 496 subjects and 520 administrations
Headache	9 (1.8%)
Musculoskeletal pain	4 (0.8%)
Fatigue	3 (0.6%)
Nausea	3 (0.6%)
Anxiety	2 (0.4%)
Back pain	2 (0.4%)
Blood pressure increased	2 (0.4%)
Claustrophobia	2 (0.4%)
Feeling cold	2 (0.4%)
Insomnia	2 (0.4%)
Neck pain	2 (0.4%)

5.6.1.2. Deaths

One death was reported during the safety reporting period for florbetapir F 18 clinical studies. This subject was an ~80-year-old, hospice dwelling, subject in the Autopsy Cohort of Study A07 who experienced severe respiratory failure resulting in death, during the 48-hour safety monitoring period. The subject had a medical history of end-stage Parkinsonism and dementia. The subject also had a relevant history of metabolic acidosis and failure to thrive with gastrostomy-tube insertion. At the time of entry into the study, the subject was noted to be undernourished and was bed-ridden and somnolent.

The subject received an injection of florbetapir F 18 and a full PET imaging scan was obtained. There were no complications during the PET imaging procedure and no indications of distress on the part of the subject. The subject was readmitted to hospice and routine care continued throughout the next day with no change in clinical status noted by the nursing staff. Approximately 30 hours after receiving florbetapir, the subject was found unresponsive. Cause of death was noted as respiratory failure. The TEAE was assessed as severe, and the relationship of the event to the study drug was considered remote (ie, unlikely).

In this end-of-life population, having an inclusion criterion of an estimated lifespan of less than 6 months, deaths were not unexpected, even occurring in close proximity to study drug administration. Notably, several subjects who were considered for possible participation in this study by the site investigators died in the few days prior to the expected enrollment in the study, highlighting the short life expectancy of this population.

Outside of the Avid-sponsored clinical studies, one additional death was reported among subjects who have been treated in ongoing trials in which florbetapir F 18 is being used as a biomarker for a therapeutic agent under pharmaceutical company IND. An ~80 year old AD patient with a history of cigarette smoking, excessive caffeine consumption, chronic obstructive pulmonary disease (COPD), hypertension and hypercholesterolemia experienced a fatal hemorrhagic stroke. The patient developed a headache, garbled speech and difficulty walking, starting one day

following his baseline florbetapir-PET scan and was taken to the emergency room where CT revealed a large occipital hemorrhage. The subject became comatose and died. The causal relationship of death to the florbetapir F 18 injection was listed by the investigator as unlikely.

5.6.1.3. Other Serious Adverse Events

In addition to the previously mentioned death, one other SAE was reported during the Avid-Sponsored clinical studies of florbetapir F 18. A subject from Study A05, an ~90 year old with a clinical diagnosis of AD, was hospitalized for a fracture resulting from a fall injury four days after imaging. The event was considered to be moderate in severity and to have a remote (unlikely) relationship to study drug.

Outside of the Avid-sponsored clinical studies, one additional serious adverse event was reported in ongoing trials in which florbetapir F 18 is being used as a biomarker for a therapeutic agent under a pharmaceutical company IND. An ~70 year old AD patient with a relevant history of prior stroke, hypertension, COPD, and hyperlipidemia experienced an acute stroke beginning one day following administration of therapeutic study medication (vs placebo; blind is preserved) and two days following the florbetapir F 18 injection and PET scan. The patient had completed the PET scan uneventfully, and then returned the next day for the protocol specified lumbar puncture. The following day the subject was randomized to therapeutic study medication. The caregiver then noted slurred speech resulting in hospital admission two days later (4 days after the florbetapir-PET scan). The patient subsequently recovered and was discharged from the hospital two days after admission. The investigator considered this SAE to be unlikely related to florbetapir F 18.

5.6.1.4. Vitals signs

Small but statistically significant increases in mean systolic blood pressure (e.g. an increase of approximately 2.5 mmHg systolic blood pressure) were seen between baseline and post dose measurements. In 10-15% of cases, the changes in individual subjects met prespecified criteria for potential clinical significance (e.g., systolic pressure >180 mmHg or an increase ≥ 20 mmHg), particularly at the 75-minute postdose measurement (i.e., at the end of the scanning procedure). In evaluating the clinical relevance of these findings, it is important to consider what is known about variability in the cardiovascular tone in a medical research environment like that in the florbetapir studies. Blood pressure and pulse are considered to have intrinsic variability based on changes in sympathetic and parasympathetic tone.²³ One well-known consequence of this dependence is ‘white coat hypertension’ which is the phenomenon of a patient having substantially increased blood pressure when the patient is being evaluated in a medical setting.^{23,24} Typically attributed to anticipatory anxiety, the elevation of blood pressure in this setting is highly variable from subject-to-subject with some reports measuring patients having a rise of 55 mmHg in systolic blood pressure with the arrival of a physician.²⁴ Consistent with this hypothesis, subjects in the florbetapir studies that had the largest post baseline changes (i.e., met criteria for potential clinical significance) had evidence for more general blood pressure variability with significant increases in blood pressure levels prior to study drug administration (i.e. the predose blood pressure was increased as compared to screening). The changes in blood pressure after study drug administration were generally not judged to be clinically significant by the site investigators and resolved without treatment. Importantly, changes in blood pressure were not related to the mass dose of compound administered (e.g., correlation of mass dose to

change in systolic BP from baseline to 75minutes: $r=0.0184$, $p=0.6293$). Supportive evidence for the lack of drug effect on blood pressure was also obtained in a preclinical safety pharmacology study in which no significant changes in blood pressure were observed in with canines given doses up to 100-fold the proposed maximum human mass dose of florbetapir (allometrically scaled).

No other notable changes in vital signs were observed in the integrated analysis.

5.6.1.5. Laboratory parameters

There were no clinically meaningful predose to postdose changes in the mean values associated with any laboratory value when considering the entire safety population or when evaluating changes by cognitive status. While some predose to postdose changes achieved statistical significance ($P < 0.05$), many moved in a non-detrimental direction (e.g. a decrease in liver enzymes). In no instance did these changes represent a pattern of laboratory value changes as would be expected in the presence of clinically meaningful organ or system toxicity. Thus, the scattered and minimal changes in clinical laboratory results do not suggest the presence of any clinically meaningful toxicity as a result of florbetapir F 18 administration.

5.6.1.6. ECGs

In the 344 subjects with pre and post dose treatment ECG measurements, the only statistically significant finding was a small (3 msec) mean increase in QTcF at the 75 minute post dose time point (shortly after completion of imaging). This change in mean QTcF may be a consequence of the algorithm used to correct for heart rate decrease rather than a true physiologic change, as the algorithm tends to under-correct when heart rate is low and produce spurious high QTc values. This is supported by the observation that the mean QTcB did not change significantly from Baseline at any post dose time point. No individuals had increases in QTcF or QTcB more than 60 msec from baseline, and no absolute QTc values exceeded 500 msec. Combined with the absence of hERG channel binding and the lack of effects on cardiovascular function in preclinical studies, these results suggest florbetapir F 18 has no significant effect on cardiac electrophysiology.

5.6.1.7. Adverse Events in Subpopulations

Adverse events, clinical laboratory investigations, vital signs and ECG were evaluated as a function of subject age, cognitive status, gender, race, comorbid cardiac rhythm disturbance (by baseline ECG), and presence of AD medications or medications that might prolong QTc. Overall there were no significant differences in clinical laboratory investigations, vital signs and ECG across any of the identified populations. Adverse events tended to be reported with the highest frequency in young cognitively normal females. However, within geriatric subjects (>65 years of age) there was no difference in frequency of adverse event reports in males, or cognitively normal versus cognitively impaired subjects, and there was no overall difference between subjects with/without cardiac rhythm disturbance, AD medications or medications that might prolong QTc. Thus, there appears to be no selective vulnerability in the likely target population of older individuals seeking diagnosis for cognitive impairment.

5.6.1.8. Radiation Safety

The human radiation dosimetry of florbetapir F 18 has been studied in three different clinical studies; two under IND (studies A01 and A02) and one foreign CTA study (Lin et al²⁵). On the whole, the results of these three studies were very comparable; with a mean human effective dose of 0.013 mSv/MBq in Study A01, 0.019 mSv/MBq in Study A02, and 0.019 mSv/MBq in the Lin et al study. Given the larger population studied in trial A02 (N = 9) and the longer image acquisition period (up to 6 hours), this trial is considered the most relevant, providing the best estimate of human radiation absorbed dose from a florbetapir F 18 iv administration. The final dosimetry results of these studies, generally, and the A02 trial specifically, have shown that the total radiation dose from a 370 MBq bolus injection of florbetapir F 18 is very comparable to that of other F-18 radiopharmaceuticals such as FDG.

5.6.2. Nonclinical safety assessments

The nonclinical safety pharmacology studies focused on the possible effects of florbetapir F 18 on the nervous and cardiovascular system.

5.6.2.1. Safety Pharmacology

Safety pharmacology studies included in vitro testing for undesired off-target binding of the nonradioactive version of florbetapir F 18 (also referred to as AV-45 or ¹⁹F-AV-45) to 46 central nervous system (CNS) and cardiovascular binding sites known to mediate pharmacological effects. The in vitro binding studies demonstrated very low affinity of AV-45 for all tested CNS and cardiovascular receptors tested, including the human ether-à-go-go-related gene (hERG) potassium channel binding site. The potential for adverse effects on the CNS was further explored by using the standard functional observational battery (FOB). No behavioral effects were observed at maximal dose levels in the single dose and repeat dose studies corresponding to 100 times and 25 times the MHD, respectively (allometrically scaled).

Cardiovascular safety pharmacology was further studied using cloned hERG potassium channels expressed in human embryonic kidney cells. At 10 µM of AV-45, the highest achievable concentration in the test system (0.3% dimethyl sulfoxide [DMSO]), there was only 17% inhibition. Therefore, no potential cardiovascular adverse effects due to AV-45 interaction with hERG and IKr currents would be expected at the MHD level of 50 µg (estimated C_{max} = 28 nM) in humans.

Cardiovascular safety and respiratory safety were also evaluated in vivo using conscious dogs and telemetric recording systems. At doses up to 128 µg/kg (100 times the MHD), AV-45 treatment had no effect on blood pressure (systolic, diastolic, and mean arterial pressure), heart rate, body temperature, electrocardiogram (ECG) parameters (heart rate and PR, QRS, RR, and QT/QTc intervals), respiratory function (respiratory rate, blood oxygen saturation, and end-tidal carbon dioxide [CO₂]), clinical observations, body weights, or mortality in young adult male or female beagle dogs.

In summary, the safety pharmacology studies did not reveal any risk of adverse effects of florbetapir F 18 on the CNS or the cardiovascular system, with NOAELs at least 100 fold higher than the maximum intended dose from a single dose of florbetapir F 18 to humans.

5.6.2.2. Toxicology

The potential toxicity of AV-45 was tested in rats with single acute doses (up to 100 times the MHD of 50 µg) and for 28 days of repeated daily dosing (up to 25 times the MHD). No clinically relevant effects were observed on behavior, gross pathology, or histology in either study. The 14-day and 28 day repeat-dose IV toxicity studies were also performed in beagle dogs, and there were no significant adverse findings based on clinical observations, weight, gross pathology or histopathology at any dose studied (highest dose levels were 8.7 times and 25 times the MHD, respectively, allometrically scaled). In each rat and dog toxicity study conducted, the NOAEL was determined to be equal to the highest dose level tested.

Potential genetic toxicity was tested in both in vitro and in vivo assays. Bacterial reverse mutation assay results showed positive responses in 2 out of 5 tested strains. The human peripheral lymphocytes (HPL) chromosomal aberration assay showed no statistically significant test article-related increases in the percent of cells with structural aberrations after 3 hours of continuous exposure, but a statistically significant positive result was seen after 22 hours of continuous exposure. In the in vivo micronucleus assay, AV-45 produced no evidence of genotoxicity when administered at doses up to the highest practically-achievable dose (83 times the MHD) for 3 consecutive days. The different results in the in vitro bacterial mutation and chromosome aberration assays and the in vivo micronucleus study are likely related to differences in the exposure conditions encountered by the target cells in the different test systems. In vivo, AV-45 is cleared rapidly; however, the in vitro experiments employ static, prolonged exposure of cells to high concentrations of the test article.

No reproductive and developmental toxicity, immunotoxicity, and carcinogenicity evaluations were conducted, given the intended single dose use of the drug product in elderly, non-pregnant individuals.

In summary, no nonclinical findings suggested a potential for adverse safety effects in humans.

5.7. Safety Conclusions

Florbetapir-PET was well tolerated in clinical studies involving 496 subjects and 520 dose administrations. The most common AE observed was headache, which occurred in less than 2% of subjects. Other notable AEs were likely related to the procedure of IV injection (<1% of subjects with injection site bleeding, bruising or pain) or to the PET-procedure (musculoskeletal pain in 0.8% of subjects). The rate of the musculoskeletal AEs was highest in studies requiring prolonged imaging times for dosimetry measurements.

There were small but statistically significant changes in lab parameters and vital signs, but most appeared non-detrimental and were likely procedural in nature (e.g., changes in pulse and blood pressure at 75 minutes, when the patient finished the PET procedure) or were likely artifactual (eg, systematic differences in methods for drawing labs [catheter vs. butterfly]). No changes in safety labs or vital sign measurements suggested toxicity of the study drug.

There was no adverse safety signal in cognitively impaired subjects as compared to cognitively normal subjects or as compared to the whole safety population. In addition, the study drug was well tolerated even in the A07 Autopsy Cohort end-of-life population which had many significant concomitant medical illnesses.

Subpopulation analyses were conducted to look for any safety effects in males vs females, in the geriatric subpopulation, in white vs non-white subjects, in subjects taking AD medications, in subjects with cardiac rhythm disturbances and in subjects taking medications that could prolong QT. There were no consistent changes in safety parameters observed in any of these subpopulations.

6. QUESTIONS RELATED TO GUIDANCE FOR USE AND INTERPRETATION

6.1. What is the definition of pathologically significant β -amyloid

There are two sets of criteria for neuropathological diagnosis of AD that are most widely used: CERAD criteria and NIA-Reagan criteria.

CERAD Criteria

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) established a standardized protocol for the neuropathological evaluation of autopsy brains and standardized criteria for diagnosis of AD neuropathology. Briefly, the CERAD criteria recommend sampling tissue from 5 anatomic regions (including neocortical regions of the frontal, temporal and parietal lobes) and the use of a stain for cerebral amyloid, such as modified Bielschowsky silver stain, thioflavine S preparation, or anti-A β antibodies. The neuropathologist should then make a semiquantitative assessment of neocortical neuritic amyloid plaques (in the area of maximum density) using the categories of "none", "sparse", "moderate" or "frequent", as shown in [Figure 8](#).

Figure 8: CERAD Neuritic Plaque Visual Scale¹

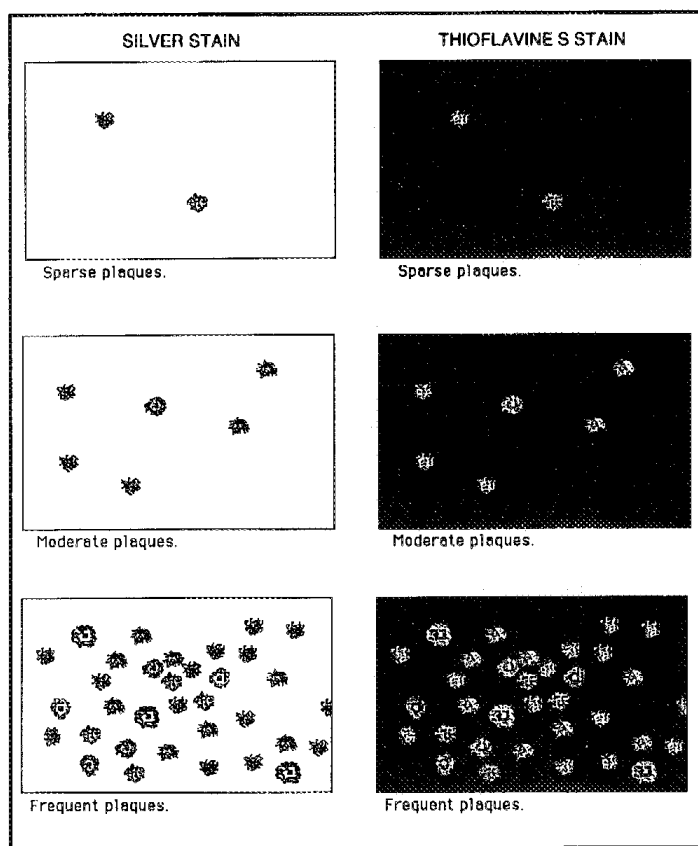


Figure 2. Senile plaques (neuritic) per 100 \times microscopic field. This cartoon provides a guide to semiquantitative assessment of plaque density per square millimeter.

The original CERAD criteria¹ then converts the plaque category assessment into a diagnosis of AD using patient age and clinical history. Generally, more than sparse neuritic plaques are needed to reach a high confidence of AD neuropathology, although any amyloid plaque pathology would be considered abnormal in subjects under the age 50. The CERAD criteria are also used in a modified-form in which the plaque category is converted directly into a neuropathologic diagnosis, notwithstanding patient age or clinical presentation.²¹ Table 18 below shows the conversion under the modified-CERAD criteria.

Table 18: CERAD Plaque Rating and Diagnosis

Modified CERAD Scoring		
Neuritic Plaque Counts	CERAD Plaque Rating	Modified CERAD Diagnosis
<1	None	No AD
1-5	Sparse	Possible
6-19	Moderate	Probable
20+	Frequent	Definite

Thus, using these criteria, more than sparse neuritic plaques are needed to reach a high probability of AD pathology. Patients who have none / sparse neuritic plaques have only a low probability of AD (none/possible).

NIA-Reagan Criteria

The National Institute on Aging (NIA) and Reagan Institute Working Group published new criteria for neuropathologic diagnosis of AD in 1997.²⁷ These criteria built on the CERAD criteria by including tangle stage (using Braak and Braak ratings²⁸) into the diagnostic assessment. The NIA-Reagan criteria rate likelihood that dementia is caused by AD using the following table.

Table 19: NIA-Reagan Autopsy Diagnosis

NIA-Reagan Criteria		
CERAD Plaque Rating	Braak & Braak Tangle Stage	NIA-Reagan Diagnosis
None	None	Not AD
Sparse	Stage I / II	Low Likelihood
Moderate	Stage III / IV	Moderate Likelihood
Frequent	Stage V / VI	High Likelihood

Similar to the modified CERAD criteria, under the NIA-Reagan criteria, the diagnosis of AD is unlikely in patients who have none/sparse neuritic plaques. In contrast, AD is likely in patients with moderate/frequent neuritic plaques.

Based on both of the widely used criteria for post-mortem diagnosis of AD, it can be seen that patients with more than sparse neuritic plaques are likely to have AD, whereas patients with sparse or fewer neuritic plaques are unlikely to have AD. Thus, the use of a test for ruling out

the presence of more than sparse neuritic plaque in vivo, in subjects with clinical signs and symptoms of cognitive impairment will, effectively, rule out the diagnosis of AD and lead to more careful evaluation and appropriate treatment for alternative causes of cognitive deficits (e.g. vascular dementia, dementia with Lewy bodies, Parkinson's dementia, geriatric depression, or medication induced impairments). In addition, the use of a test for ruling in the presence of abnormal levels of β -amyloid pathology in subjects with signs and symptoms of cognitive impairment will lead to the selection of patients who warrant more detailed work-up for the possible diagnosis of AD or MCI. For this reason, it is important to know whether or not a patient has more than sparse neuritic plaques.

6.2. What is the β -amyloid Threshold for Florbetapir F 18 Positivity

Imaging and pathology results are shown for the 35 subjects who came to autopsy in the A07 trial in [Table 20](#) below. Cases are sorted by amyloid burden (% area occupied by amyloid pathology by immunohistochemistry) and a pseudo-color scale is applied to this column. Other cells are colored as green (for negative results by pathology or imaging) or as red (for positive results by pathology or imaging). These results suggest that florbetapir-PET scans become positive (either by $\text{SUVR} > 1.1$ or visual read semi-quantitative score > 1) when more than sparse neuritic plaques are present. This corresponds to a total amyloid burden of approximately $> 1\%$ by immunohistochemistry. In one patient with 1.11% amyloid burden by IHC there were only diffuse plaques (064-055) and this patient had a negative CERAD rating ("None") and a negative PET scan.

Table 20: Histopathology Imaging Results Table

SubjID	CERAD Neuropath Diagnosis	CERAD Neuritic Plaque Category	CERAD Average Plaque Score*	IHC % Amyloid Burden	Median Visual Read	SUVR
054-002	No AD	None	0.00	0.00	1	1.09
060-014	No AD	None	0.00	0.00	1	0.92
145-019	No AD	None	0.00	0.00	1	1.00
217-006	No AD	None	0.00	0.01	0	0.93
054-010	No AD	None	0.00	0.01	0	0.88
057-007	No AD	None	0.00	0.01	1	0.91
066-021	No AD	None	0.00	0.01	0	0.88
059-003	No AD	None	0.00	0.01	0	1.07
217-001	No AD	None	0.00	0.01	0	0.87
061-010	No AD	None	0.00	0.02	1	0.81
152-001	No AD	None	0.42	0.03	1	0.92
062-001	No AD	None	0.50	0.04	0	1.09
054-003	No AD	None	0.00	0.15	0	0.87
064-001	Possible	Sparse	0.92	0.47	0	1.00
061-001	Possible	Sprase	0.58	0.49	0	0.98
064-005	No AD	None	0.00	1.11	1	1.00
522-001	Probable	Moderate	1.33	1.11	3	1.64
062-004	Definite	Frequent	2.75	1.42	3	1.21
217-003	Definite	Frequent	2.00	1.48	3	1.39
132-001	Probable	Moderate ^a	0.67	3.27	4	1.45
134-001	Definite	Frequent	1.92	3.42	3	1.40
057-002	Definite	Frequent	2.42	3.63	2	1.17
134-006	Definite	Frequent	2.83	4.67	3	1.38
522-003	Probable	Frequent	2.00	4.85	1	1.23
053-001	Definite	Frequent	2.08	5.27	3	1.20
145-007	Definite	Frequent	3.00	5.31	3	1.36
134-004	Probable	Frequent	1.75	5.38	4	1.91
060-004	Definite	Frequent	2.61	5.39	3	1.56
066-001	Definite	Frequent	2.50	5.61	4	1.63
217-005	Definite	Frequent	1.75	6.69	4	1.34
522-005	Definite	Frequent	2.92	7.01	3	1.20
145-001	Definite	Frequent	2.33	7.92	4	1.38
134-002	Definite	Frequent	2.56	8.62	4	1.66
522-008	Definite	Frequent	2.25	9.11	3	1.37
137-005	Definite	Frequent	3.00	9.44	4	1.57

^a Subject 132/001: 8 neuritic plaques identified, Mid Frontal Gyrus 2 (L-1 MF2 11).

* CERAD average score is the average of each regional CERAD score (converted to a number).

Therefore, results from the 35 autopsy cases in the A07 clinical trial indicate that the presence of more than sparse neuritic plaques (i.e. CERAD moderate / frequent) is required before a scan becomes positive (either by visual interpretation or by SUVR analysis). Thus florbetapir does not detect the presence of only sparse neuritic plaques, nor does it detect the presence of diffuse plaques only. Thus, a negative scan should be interpreted to indicate the absence of *significant* (more than sparse) neuritic amyloid plaque pathology.

6.3. What is the recommendation for how imaging specialists should interpret florbetapir-PET scans?

It is recommended that imaging specialists should interpret florbetapir-PET scans in a binary manner indicating whether the scan is positive or negative for beta-amyloid deposits. The basis for this recommendation is that a negative florbetapir-PET scan is most consistent with the absence of pathologically significant levels of amyloid deposits while a positive scan is most consistent with the presence of pathologically significant levels of amyloid (see 6.1 above). Information regarding pathologically significant levels of β -amyloid could be important to the patient's referring physician since the presence or absence of such levels are tied tightly to pathological diagnosis of Alzheimer's disease. Thus, the absence of pathologically significant beta-amyloid by florbetapir-PET scan would make a pathological diagnosis of Alzheimers disease unlikely. Depending on the clinical setting, the presence of pathologically significant beta-amyloid would suggest the presence of a pathological diagnosis of Alzheimers disease. Therefore, both negative and positive scan interpretations would have utility in the proper clinical settings.

6.4. How do the results of the correlational analysis in the Phase III study help the imaging specialists interpret florbetapir-PET scans?

The correlational analysis between the visual rating of the florbetapir-PET scan and the levels of beta-amyloid seen at autopsy, a primary endpoint of the Phase III study, demonstrated the efficacy of florbetapir F 18 as a molecular imaging tracer for detection and quantitation of β -amyloid deposits. These data give confidence to the imaging specialist interpreting the scans, and the referring physician incorporating the scan results into their diagnostic information, in that the radiopharmaceutical is a validated PET molecular imaging tool.

The correlational analysis relied on visual interpretation using a semi-quantitative scoring (0-4) of florbetapir-PET scans by three nuclear medicine physician readers that had undergone a brief (1/2 day) training. The median ranking of the three readers, as well as the rankings from each of the three individual readers, all correlated quite well to post-mortem pathological levels of β -amyloid. Thus, imaging specialists interpreting florbetapir-PET should also have confidence that with similar levels of training they should be able to use their visual interpretation to correctly rank the scans with respect to the overall levels of amyloid.

6.5. What data indicates that imaging specialists can perform accurate binary interpretation of florbetapir-PET scans?

In the Phase III study there were two primary endpoints; each associated with a specific dataset. One dataset was from a group of three readers that interpreted florbetapir-PET scans with a semi-quantitative scale to allow a correlational analysis to the measured levels of β -amyloid at autopsy. There was a second dataset from a different and independent set of three readers that interpreted florbetapir-PET scans in a binary read to evaluate the specificity of florbetapir-PET scans, including scans from patients who later went to autopsy as well as from young healthy controls expected to have no amyloid. Both of these datasets are highly informative as to the expected accuracy of imaging specialists interpreting florbetapir-PET scans in the future.

The correlational analysis did not include any binary interpretation of the scan by the readers, however, an exploratory analysis included deriving a binary interpretation by parsing the ratings using a prespecified rule: 0 and 1 would indicate a negative reading; while 2, 3 and 4 would indicate a positive reading. When the median rankings of the three readers were used, the resulting derived binary interpretations were highly accurate predictions of whether pathologically significant levels of amyloid were seen at autopsy. (See 6.2 above) In the 29 scans used in the efficacy dataset, 14/15 (94%) of the patients who had significant levels of amyloid (e.g., more than 'sparse' on CERAD) were identified as positive. All 14 patients in the autopsy cohort primary analysis population who had less than significant levels of amyloid (none or sparse on CERAD) were identified as negative. Thus, 28 of 29 scans had derived binary reads that accurately predicted pathology.

Table 21: Agreement Between Florbetapir-PET and CERAD

Florbetapir-PET Image Outcome:		Reference Standard:		
		CERAD		
		Positive (Moderate, Frequent) (N=15)	Negative (None, Sparse) (N=14)	
Semi-quantitative Visual Blinded Read	Positive (2,3,4)	14	0	PPV = 100%
	Negative (0,1)	1	14	NPV = 94%
		Sensitivity = 94%	Specificity = 100%	Accuracy = 97%

For the scans in which binary reads were done directly (the 'specificity' reads), and did not have to be derived from semi-quantitative scores, there were similarly good results. For analysis of this data the primary endpoint was using the majority read from the three readers. The majority read was negative in all 47 of the 47 florbetapir scans in the young healthy APOE ϵ 4 negative subjects. In addition, these readers interpreted 40 scans from the autopsy cohort that had a

median ranking of 2, 3 or 4 by the three readers in that study (i.e, they had a derived binary interpretation of positive). The ‘specificity’ readers interpreted 38 of these 40 autopsy cohort scans also as positive, indicating that direct binary interpretation was very similar (95%) to the derived binary interpretations. Furthermore, 14 of these 40 scans were from patients that ultimately underwent autopsy. In all 14 of these patients the majority binary interpretation was positive and the autopsy evaluation of β -amyloid levels showed pathologically significant levels of amyloid (CERAD neuritic plaque density greater than sparse).

Thus, the primary analysis for the binary ‘specificity’ reads, and the derived binary reads from the rankings in the correlational reads, indicate that it is clearly possible to obtain highly accurate binary interpretations of florbetapir-PET scans.

6.6. What is the data indicating that individual imaging specialists can perform accurate binary interpretation of florbetapir-PET scans

Both primary endpoints in the pivotal Phase III study used the median, or majority, read from three readers. This was done to ensure the analysis yielded the most accurate representation of the efficacy of Florbetapir F 18 as a molecular imaging tracer. If approved, however, Florbetapir F 18 will generally be interpreted by a single imaging specialist. Thus, it is relevant to examine the individual reader performance for both direct binary reads and derived binary reads.

In direct binary reads each of the three readers performed excellently. First, when all reads were combined there was excellent reader agreement as shown by high percent agreement and high kappa statistics. (See [Table 22](#))

Table 22: Specificity Agreement

Specificity Readers	Observed agreement	Kappa Statistic
Reader 4 vs Reader 5	94%	0.86
Reader 4 vs Reader 6	99%	0.98
Reader 5 vs Reader 6	93%	0.84

When individual reader binary interpretations were compared to the truth standard, accuracy for the three readers was very high. In identifying the amyloid negative cases the accuracy results for the three readers were 100%, 98%, and 100% (see [Table 23](#)).

Table 23: Specificity Results

Specificity Readers	Read Negative / Presumed Negative	%
Median	47 / 47	100%
Reader 4	47 / 47	100%
Reader 5	46 / 47	98%
Reader 6	47 / 47	100%
<i>All Reads</i>	<i>140 / 141</i>	<i>99%</i>

For those scans that had autopsy data the three readers also did very well. The accuracy in identifying the presence of pathologically significant amyloid was 100%, 93%, and 93% (see [Table 24](#)).

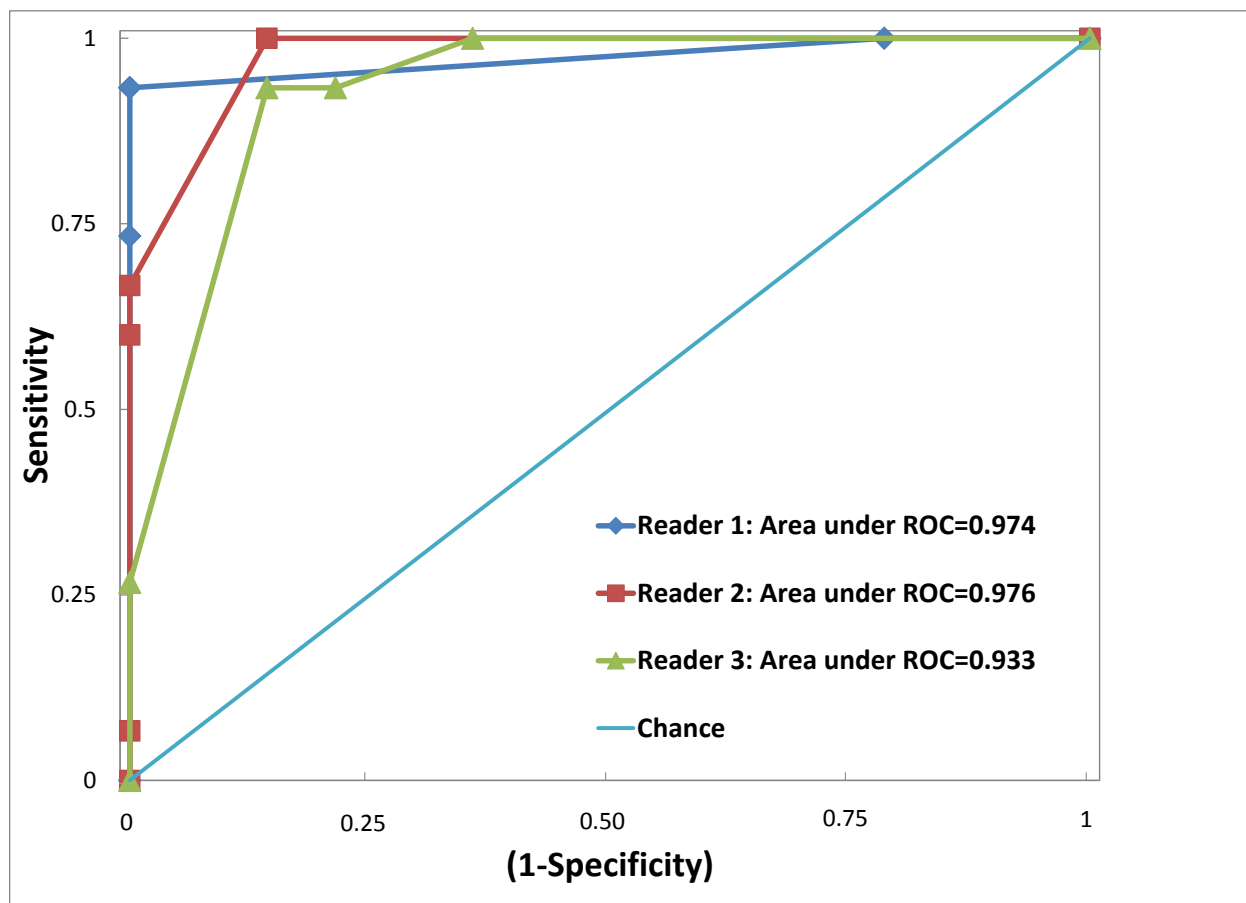
Table 24: Sensitivity in Specificity cohort

Specificity Readers	Read Positive / CERAD > Sparse	%
Median	14 / 14	100%
Reader 4	14 / 14	100%
Reader 5	13 / 14	93%
Reader 6	13 / 14	93%
<i>All Reads</i>	<i>40 / 42</i>	<i>95%</i>

In the correlation analysis the individual readers rated each scan on a semi-quantitative scale (0-4). However, there was no pre-specified threshold for deriving a binary read on the individual ratings. In lieu of a pre-specified threshold, an alternative is to examine the receiver operating characteristic (ROC) curves for each reader (see [Figure 9](#)). The generation of the ROC curve for a given reader requires that all possible thresholds for deriving a binary interpretation are used and the results for each threshold compared to the presence of pathologically significant levels of amyloid plaque (by > sparse on CERAD). Inspection of the figure below shows the ROC curves

all have high areas (Reader 1 = 0.974; Reader 2 = 0.976; Reader 3 = 0.933) indicating that a derived binary interpretation has high diagnostic power in each individual reader.

Figure 9: ROC curves for presence or absence of significant β -amyloid by CERAD: Binary read derived from each reader's semi-quantitative scores in the efficacy dataset.



In summary, the data strongly indicate that individual readers can interpret florbetapir-PET scans in a binary fashion with high accuracy. From the dataset using direct binary reads the individual readers were internally consistent and all had high accuracy (> 90%) compared to truth standards. The dataset requiring derived binary interpretations from the semi-quantitative whole brain rankings did not have prespecified thresholds, however, each reader showed very good accuracy as judged by their ROC curve (mean area under ROC \pm S.D. = 0.961 ± 0.024). The high areas under the ROC indicate that the readers were able to rank the PET scans quite well in regards to the likelihood the patient had pathologically significant amyloid at autopsy. However, it should be pointed out that all readers underwent a formal training program and thus it is likely that training of imaging specialists to interpret florbetapir-PET scans using a binary read will likely be important to assure consistency across readers and scans.

7. GUIDANCE FOR USE

7.1. Dosing

The recommended single intravenous dose for Florbetapir F 18 Injection is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of ≤ 10 mL. This dose, in a blinded read of Florbetapir-PET scans, provided consistent good quality PET images from a 10 minute scan acquisition. No special preparation of the patient is needed. The florbetapir F 18 dose is administered by intravenous injection, followed by a flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose. The effective radiation dose from a 370 MBq i.v. administration of florbetapir F 18 was studied in the ^{18}F -AV-45-A02 trial, which was conducted in 9 healthy volunteers who were imaged for up to 6 hours after injection. Most organs received between 0.005-0.03 mSv/MBq, but the primary excretory organs for florbetapir F 18, the liver, gallbladder, small intestine and upper large intestine, received a radiation dose of between 0.06-0.14 mSv/MBq. The mean total body dose for the nine subjects in the study was 0.012 ± 0.001 mSv/MBq and the mean effective dose was approximately 0.019 mSv/MBq or 7.0 mSv (0.7 rem). Modeling urinary bladder voiding at 90 minutes post injection did not significantly change the radiation dosimetry. Where studies are performed on a PET/CT scanner, additional radiation exposure may result (as much as 2 mSv) from the CT component, which is used for attenuation correction and structure location. Thus, the total expected radiation exposure for florbetapir F18 PET studies may be up to 9 mSv, when performing PET/CT. This is similar to or less than a comparable dose of the widely-used radiopharmaceutical ^{18}F -FDG with PET/CT imaging.

7.2. Imaging

A 10 minute brain PET image (acquired as 2 x 5 minute scans with scatter correction) is recommended as this provided good quality PET scans in clinical trials of florbetapir F 18. The PET image can be acquired starting at any time between 30 and 80 minutes after intravenous injection. Comparable cortical to background signal ratios were observed in the A03 and A06 studies of florbetapir F 18 with a 10 minute image obtained at any point during this 30-90 minute period following dose administration. When acquiring florbetapir-PET images, the head should be positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reconstruction should include attenuation correction with an external transmission source or low dose CT scan.

7.3. Image Interpretation

7.3.1. Training

Avid proposes to make training images, including images taken from the Phase III trial along with the CERAD plaque scores acquired at autopsy, available at a training website. It is recommended that a new user of Florbetapir F 18 Injection for amyloid PET imaging should complete the training modules provided on this website or complete similar training available

from other professional organizations or medical education providers. In addition, this training website will provide links to other important resources and literature to aid the nuclear medicine and radiology physician become more familiar and competent with the assessment of florbetapir-PET scans.

7.3.2. Effect of Clinical Information on PET Scan Interpretation

In clinical trials of florbetapir-PET, the blinded image readers evaluated the images without access to clinical information associated with the subject's scan. Although access to clinical information typically improves the readers' accuracy of diagnostic image evaluation²⁶, it is not known whether clinical information might influence image interpretation of florbetapir-PET scans. Therefore, it is recommended that image interpretation should be done in such a manner as to minimize the impact of clinical information.

7.3.3. Image Evaluation

As noted in Section 6 of this Briefing Document, both binary (+ / -) and semi-quantitative visual interpretation of florbetapir-PET images were conducted in clinical trials with good results in the blinded reader image interpretations.

For routine clinical use the binary (i.e. positive or negative) image assessment of Florbetapir-PET scans provides a reliable and accurate assessment of the presence or absence of pathologically significant levels of β -amyloid levels in the brain. The high specificity of the florbetapir-PET scan observed in the Phase III A07 trial using the binary image rating score indicates that a negative florbetapir-PET scan is consistent with the absence of significant levels (e.g. CERAD neuritic plaque density of none to sparse) of β -amyloid levels in the brain.

8. CONCLUSION

Florbetapir F 18 is a novel ^{18}F labeled amyloid imaging agent designed to image the amyloid pathology that characterizes Alzheimer's disease. Florbetapir has now been used for research purposes in more than 2,000 patients across approximately 100 imaging sites on 5 continents. Ongoing research studies include numerous therapeutic pharmaceutical trials (where florbetapir is used as a biomarker for patient selection or surrogate endpoint), longitudinal studies of aging and disease (including the Alzheimer's disease neuroimaging initiative, ADNI), and investigator initiated studies.

NDA #202-008 reports the results of 7 completed studies conducted under Avid's INDs, which involved 496 subjects and provide the primary safety and efficacy data to support regulatory approval of florbetapir. **Taken as a whole, the totality of the data obtained in these 7 regulatory trials support the safety and efficacy of florbetapir as follows:**

SAFETY

- Adverse events (AEs) were reported in 9.6% of all subjects receiving Florbetapir F 18 Injection and only one case of a severe AE in the 496 subjects was reported. The AEs were infrequently considered treatment-related (3%). The most common AEs included headache (1.8%), muscle pain (0.8%), fatigue (0.6%) and nausea (0.6%). No other AEs were experienced by more than 2% of the population.
- There was one serious adverse event (SAE): Limb fracture four days post imaging.
- There was one death: A subject with end-stage Parkinson's disease who was enrolled in the autopsy cohort, died of respiratory failure approximately 30 hours after imaging.
- There was a mild and transient increase in blood pressure (2.5 mmHg systolic) related to dose / procedure. This mean increase was not correlated with the mass dose of florbetapir (F 19) injected.
- Other changes in vital signs, lab parameters, and ECGs were generally mild and non-detrimental.

EFFICACY

- All primary and secondary efficacy endpoints were met in each trial.
- The image-to-autopsy correlation study ("A07") was carried out in accordance with advisory committee (October 2008) and FDA agreement, and showed:
 - Strong, significant correlation between median visual read and amyloid burden measured by immunohistochemistry (primary analysis, n=29)
 - Strong and significant correlations obtained using other measures of PET efficacy (single reader results, regional reads, computer analysis [SUVR]) (n=35)
 - Strong and significant correlations obtained using other measures of amyloid as the reference standard (neuritic plaque counts, CERAD category) (n=35)

- The threshold for florbetapir-PET detection of β -amyloid pathology was found to be more than sparse neuritic plaques; which closely matches the pathological criteria for “significant” brain amyloid pathology.
- The specificity analysis revealed no false positive scans in young healthy controls (n=47).
- Phase II results demonstrated the expected associations between florbetapir-PET results and factors known to be associated with brain amyloid pathology:
 - The rate of positive scans observed in AD, MCI, and HC subjects matched literature autopsy results for true prevalence of amyloid pathology in these populations
 - The rate of positive scans observed in HC subjects showed the expected age dependency, matching literature autopsy results
 - The rate of positive scans was highest in subjects carrying the ApoE e4 allele, matching literature autopsy results
 - Amyloid deposition was found to be the single most significant risk factor for poorer cognitive performance in otherwise cognitively normal elderly controls (HCs).
- Phase II results demonstrated florbetapir-PET to be reliable for routine clinical practice:
 - Single 10 mCi dose, given by IV injection
 - 10 minute scan, 30 to 90 minutes post injection
 - High level of test-retest reproducibility (~95% for quantitation)

The clinical and non-clinical data regarding florbetapir F 18 presented in the NDA support the proposed indication and usage statement:

“Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β -amyloid in the brain.”

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